A REVIEW OF THE EPIDEMIOLOGY OF ETS AND LUNG CANCER

Peter N Lee

P.N.Lee Statistics and Computing Ltd

17 Cedar Road

Sutton

Surrey, SM2 5DA

UK

April 1997

EXECUTIVE SUMMARY

It has been suggested that epidemiological studies of lung cancer in nonsmokers support the hypothesis that environmental tobacco smoke (ETS) causes lung cancer. This document examines this suggestion in detail, presenting an extensive review of the epidemiological evidence.

Data from 46 epidemiological studies of ETS and lung cancer among lifelong nonsmokers have been considered. All the studies concern females, with 15 also providing data for males. A variety of indices of ETS exposure have been used in these studies. Nearly all consider smoking by the spouse (or partner) as a measure of exposure, with a number of studies considering ETS exposure by other household members, in the workplace, in childhood or in social situations.

With the exception of smoking by the husband, the overall evidence shows no significant association between lung cancer and any index of ETS exposure. However there is a highly significant ($p<0.001$) association between smoking by the husband and risk of lung cancer, with a meta-analysis of the covariate adjusted estimates from the individual studies giving a combined relative risk of 1.16 (95% confidence interval [CI] = 1.09-1.25). This apparent association shows some elements of a dose-response, with many of the studies finding risk to be highest for the highest categories of reported consumption and/or duration of smoking by the husband. Because of this, and because the ETS inhaled by nonsmokers and the mainstream smoke inhaled by smokers contain many chemicals in common, some might conclude that a causal relationship is not only plausible but has been demonstrated. Indeed random errors in determining the smoking status of the husband and in diagnosing lung cancer, coupled with the fact that women married to nonsmokers generally do have some ETS exposure, might be thought to allow the inference that the true relationship of ETS with lung cancer is actually stronger than indicated by the relative risk estimate of 1.16. However, the in depth and detailed analysis presented here undermines these conclusions and inferences.

Among points emphasized in this review are the following:

- **Existence of a risk cannot be inferred from the chemical composition of ETS**. Concentrations of chemicals in ETS are typically many times lower than permissible limits approved by regulators, and the majority of toxicologists no longer believe in the zero threshold for carcinogenesis.
- **Experimental evidence of a carcinogenic effect of ETS is lacking**.
- **The epidemiological evidence shows no significant association of lung cancer risk with other indices of ETS exposure**. The overall data, which are now quite extensive, show no indication of an increased risk in relation to ETS exposure in the workplace, in childhood, in social situations or non-spousal exposure at home. Although meta-analysis shows some evidence of an increase in risk in nonsmoking men associated with smoking by the wife, this is also not significant (relative risk 1.24, 95% CI 0.98-1.57, $0.05<p<0.1$).

It is also evident that estimates of risk in relation to smoking by the husband vary highly significantly between studies. The combined results:

- **vary significantly over time**, with no significant association evident in studies published in the 1990s;
- **vary significantly by region**;
- **vary significantly by study size**, with the association weakest in the largest studies;
- **show a tendency for risk estimates to be higher in studies judged** (by one set of criteria) **to be of "inferior quality";**
- **vary significantly, within case-control studies, by the type of control group used**, with no significant association evident in those studies using healthy population controls; and
- **show a stronger association in studies that have not properly accounted for age in design and analysis**.

Furthermore it is apparent that:

- there is a lack of consistent relationship of ETS with any specific histological type of lung cancer.

A number of methodological problems may explain the weak association and dose-response for spousal smoking. These include:

- **misclassification of current or former smokers as lifelong nonsmokers**. Detailed analyses show that bias arising from this is an important determinant of the association reported with smoking by the husband.
- **uncontrolled confounding by other risk factors for lung cancer**. Data are presented demonstrating that, in nonsmokers, ETS exposure is associated with increased exposure to a wide variety of risk factors. Furthermore lung cancer relative risks for smoking by the husband are substantially higher in studies that have not taken confounding variables into account.
- **publication bias**. The stronger association seen in smaller than larger studies is consistent with failure to publish small studies that show no association. It is also clear that studies not finding an association with spousal smoking are much less likely to present dose response data.
- **recall bias**. The overall evidence relating to spousal smoking arises predominantly from case-control studies in which data on ETS exposure are collected after the lung cancer has occurred. Biased reporting of extent and duration of exposure may affect dose-response analyses.

When all these points are considered, it is clear that the inference of a causal relationship is not justified from the available evidence. The data are in fact quite consistent with the absence of a genuinely elevated lung cancer risk arising from exposure to ETS.

This review also contains a critique of earlier reviews by other authors, highlighting major weaknesses in the arguments they put forward to claim the existence of a causal relationship.

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Appendices

1. Introduction

1.1 Objectives

The objective of this review is to provide a comprehensive compilation, analysis and interpretation of the epidemiological data on Environmental Tobacco Smoke (ETS) exposure and lung cancer.

1.2 Need for a further review

This document is particularly concerned with data from 46 studies [1-46]. While many previous reviews of the evidence have been published [e.g. 47-61], there are a number of reasons why a further review is felt necessary. First, the data have been rapidly accumulating, rendering earlier reviews out-of-date. While this is particularly true for the reviews published in the 1980's [47-52], it also applies to the EPA report [53] with 15 new studies reporting results since its publication [31-35,37-46] and one large study reporting updated findings [36]. Second, the great majority of reviews have restricted their attention to spousal smoking as an index of ETS exposure, ignoring the now quite substantial information relating to other sources of ETS exposure. Third, inadequate attention has generally been given to the various sources of bias that could affect the observed association of ETS and lung cancer. Fourth, the fact that the observed association varies markedly with various factors, such as location, size and time of publication of the study, has not emerged from most of the published reviews. Finally, the conclusions of the reviews have varied, with some of the recent reviews concluding a relationship has been established [53,55,56,58,59] and others concluding it has not been [54,57,60,61].

1.3 Structure of the review

Section 2 of this review concerns the materials and methods used, including the criteria used for selecting and rejecting studies and data, and the content of the tables and meta-analyses used to summarize the data.

The main characteristics of the 46 studies selected are summarized in Section 3 and described in more detail in Appendices.

The data relating lung cancer in nonsmoking women to smoking by the husband,

the most commonly used index of ETS exposure, are considered in detail in Section 4.

Data on smoking by the wife, smoking by the spouse, other indices of household exposure, workplace ETS exposure, childhood ETS exposure, social ETS exposure, total ETS exposure and multiple sources of ETS exposure are considered in Sections 5 to 12 respectively.

The overall data are interpreted in Section 13, with attention drawn to some weaknesses of earlier reviews in Section 14.

Following acknowledgements in Section 15 and references in Section 16, the Tables of results are presented. Finally, a number of Appendices provide additional detail.

2. Methods

2.1 Selection of studies

Relevant studies were obtained from previous reviews updated by a literature search. All data identified by the end of 1996 are included in this review.

Following precedent, attention was generally restricted to studies of lifelong nonsmokers. There are three reasons for this. First, the great majority of the epidemiological evidence concerns never smokers. Second, there is little public concern about possible effects of ETS on the health of smokers. Third, in view of the strong association of active smoking with lung cancer risk, it is likely to be extremely difficult to detect reliably any possible effect of ETS exposure in the presence of a history of smoking [54]. Exceptionally, and also following precedent, a few of the studies selected include a proportion of occasional smokers and/or long-term ex-smokers.

For a number of reasons, results from certain other studies, which might have been thought to report relevant data, were not considered. The reasons for exclusion include the following:

(a) the results were not presented separately for lifelong nonsmokers;
(b) the study had no control population;
(c) the controls were clearly unrepresentative of the population at large in respect of smoking habits;
(d) there were less than five lung cancers in lifelong nonsmokers; and
(e) the study was merely a review of data from other studies that are included.

Details of the excluded studies, with their reasons for rejection, are given in Appendix A. Appendix A also provides further references relating to the 46 studies selected. Generally, these references provide no relevant data, additional to those given in the 46 references cited in the main body of the report [1-46].

It should be noted that the set of studies selected is generally in line with that of other reviews. For example, all the studies providing spousal smoking relative risks considered by the EPA [53] are included, and our list of studies is very close to that

considered in the recent review by a European Working Group [60].

2.2 Exposure indices and extraction of relative risk data

With the exception of one study which related subsequent lung cancer risk to urinary cotinine levels determined at the start of the follow-up period [41], indices of ETS exposure have been based on questionnaire responses.

An attempt has been made to extract all relevant relative risks and 95% confidence intervals (CIs) from the published sources, not only for spousal smoking, but also for household, childhood, workplace, social and total ETS exposure. Where studies present appropriate data on numbers of cases and controls for the various exposure categories, relative risks and 95% CIs are calculated, or checked, using the CIA program based on the methods described by Morris and Gardner [62] and made available by the British Medical Journal. For some studies 95% confidence limits are calculated from 90% confidence limits presented by the authors. Appendix B gives further details of how the cited data were extracted from the source references. All data extracted were independently checked.

2.3 Adjustment for covariates

In the tables presenting the main results relating to the six major indices of ETS exposure (Table 2 - husband, Table 10 - wife, Table 16 - workplace, Table 18 - childhood, Table 20 - social, Table 22 - total) relative risks and CIs are presented both unadjusted and adjusted for covariates. In other tables relative risks presented (and in some cases also CIs) are adjusted for covariates, if adjusted data are available, and otherwise are unadjusted. Where, in some studies, the source publication provides more than one adjusted estimate, the data that are adjusted for most covariates are normally presented. Appendix C gives details of the covariates taken into account in the analyses presented.

2.4 Correction* for smoking habit misclassification

For data relating lung cancer to smoking by the husband, relative risks and 95% confidence limits are also presented corrected for smoking habit misclassification using the methods of Lee and Forey [63]. Appendix D gives details of the data used in the misclassification corrected analyses. Plausible levels of misclassification rates were taken from the recent review of published literature on the subject by Lee and Forey [64].

2.5 Meta-analysis

Combined estimates of relative risk from unadjusted and covariate adjusted results for the various indices of exposure are estimated by fixed effects meta-analysis [65]. In the case of husband's smoking fixed-effects meta-analysis is also applied to various subsets of results and to misclassification-corrected relative risks. Because the fixed-effects method takes no account of other differences between studies, e.g. in study quality or the precise index of exposure used, these combined relative risk estimates should be interpreted with caution, particularly when there is significant heterogeneity in the individual risk estimates being combined. For the ETS/lung cancer analyses that show heterogeneity, the preferred method of approach is to look for the sources of the heterogeneity, as recommended in the recent guidelines of an expert working group [66]. However, on some occasions, results of random-effects meta-analyses are also presented, based on the likelihood approach of Hardy and Thompson [67].

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*In order to avoid confusion in some situations, we use the distinct terms "correction" and "adjustment" to refer to attempts to remove bias resulting from, respectively, bias due to misclassification of smoking habits and bias due to confounding by other risk factors.

3. Study characteristics

3.1 Introduction

The review focuses on 46 studies of lung cancer and ETS exposure for which results have been separately presented for lifelong nonsmokers [1-46]. Table 1 gives details for each study of the first author of the main publication describing the results of the study, its year of publication, the location of the study, the type of study design used, and the total number of lung cancers studied in female and male lifelong nonsmokers. Appendix E gives details of further study characteristics, while Appendix F briefly describes the larger studies, involving over 100 cases of lung cancer in never smokers, and comments on their strengths and weaknesses. Summarized below are some main impressions to be gained from this material.

3.2 Dates of publication

This first two studies to present data on ETS and lung cancer were the interim reports, in 1981, from the Hirayama and Trichopoulos studies, both of which published updated results during the following two or three years. The number of published studies has grown rapidly, from 12 by 1986 to 29 by 1990 to 46 now. Four recent studies listed appeared during 1996 in a single issue of the journal "Lung Cancer" based on proceedings of a conference which took place in Guangzhou, China in 1994.

3.3 Location

Seventeen studies have been conducted in the USA, nine in Europe and 20 in Asia. No study has been reported from Australasia, Africa or South America. The relatively large number of studies in Asia, five in Japan, four in Hong Kong, one in Korea and 10 in China, may reflect the reported high incidence of lung cancer in nonsmoking women there [16]. While most of the European studies have been conducted in Western Europe (UK, Sweden, Germany or Holland), two have been conducted in Greece and one in Russia.

3.4 Study type

Five of the 46 studies were of prospective design, with data on smoking habits, ETS exposure and other risk factors collected on individuals who were then followed up

for some years for subsequent incidence or death from lung cancer. The remaining 41 studies were of case-control design, with the smoking, ETS and risk factor data collected after onset of disease in the cases. Exceptionally, three of the 41 case-control studies were nested within prospective studies with some of the data collected before onset of disease. In 17 of the 41 case-control studies healthy population controls were used, while in 20 the controls selected were patients (or decedents) suffering from diseases other than lung cancer (in most cases diseases considered to be unrelated to smoking). In two case-control studies both healthy and diseased controls were used, while in the remaining two the source reference did not define the control group.

3.5 Cases

Overall, the 46 studies collected data on 5480 lung cancer cases in lifelong nonsmoking females and on 473 lung cancer cases in lifelong nonsmoking males. The much higher number of cases in females reflects the fact that there are more female than male lifelong nonsmokers in the population (particularly in Asia). This means that nonsmoking women with smoking husbands will be much more frequent than nonsmoking men with smoking wives, so making it much easier to conduct a study of possible spousal smoking effects in females. It can be seen that, while all 46 studies collected data for females, only 15 did so for males. While 16 studies of females involved over 100 cases in females, only one study (that of Cardenas, published only as a thesis) in males did. It can be seen from Table 1 that two of the five prospective studies involved very small numbers of cases, reflecting the fact that it takes a very large prospective study indeed to obtain reasonable numbers of cases. Both the Garfinkel 1 and Cardenas studies involved interviewing over a million men and women at the start, while the Hirayama study involved over a quarter of a million. The number of cases studied is well over 2000 in both the USA and Asia, but much smaller in Europe, with only the Zaridze study in Moscow involving over 100 cases.

Twenty of the 46 studies insisted on histological confirmation of lung cancer for all cases. While there were two studies (Correa, Koo) which only very rarely accepted cases without histological confirmation, there were a substantial number of studies where a relatively large proportion, often 40% or more, accepted cases based on radiological,

cytological or clinical evidence. Insistence on histological confirmation was typical for the US case-control studies, but was not seen in any of the Western European case-control studies. With the exception of the small Butler study, which only included histologically confirmed cases, the prospective studies all relied on death certificates for their diagnosis of lung cancer. Results were presented subdivided by histological type in only about one-third of the studies.

3.6 Interviews

In many of the studies both cases and controls were interviewed directly. However, in some studies where cases were dead or too ill to be interviewed, the questions were answered by another person, usually the next-of-kin. In some studies care was taken to match cases interviewed through next-of-kin with controls interviewed through next-of-kin. This was not always so. In a number of studies (see Tables E1 and E2), all conducted in the USA, the proportion of next-of-kin respondents was clearly higher for cases than for controls. This included the very large Fontham and Brownson 2 studies where next-of-kin respondents were used for 37% and 65% of cases and not at all for controls.

3.7 Data on ETS exposure

In virtually every study, current and past ETS exposure were assessed indirectly by questions on the smoking habits of the subject's spouse, parents, cohabitants, or coworkers, or by the subject's semiquantitative assessment of the extent of exposure in certain situations. Although there are no currently available methods of objective quantification of lifetime ETS exposure, it is important to note that none of the studies attempted to quantify even current ETS exposure objectively by, for example, measuring particulate matter, nicotine or carbon monoxide in air and only one has attempted to quantify it by use of a biomarker. This was the de Waard study, which was a case-control study nested within a prospective study in which cotinine had been measured in urine at the start of the follow-up period when the subjects were cancer free. However, this study provided data on only 23 lung cancer cases in nonsmokers.

In 44 of the 46 studies, data were collected on smoking by the husband or a

closely equivalent index. Other indices of ETS exposure considered in this report were less frequently studied - smoking by the wife (15 studies), ETS exposure in the workplace (17 studies), ETS exposure in childhood (18 studies), ETS exposure in social situations (six studies) and total ETS exposure (15 studies).

3.8 Confirmation of smoking status

The great majority of the studies collected data from only one source on the smoking habit of the subject, making no attempt to confirm that the subject was indeed a lifelong nonsmoker. Only two studies used biochemical measures to try to corroborate current smoking status, both using urinary cotinine. In the de Waard study (which, as noted above, also used the cotinine measurement to assess ETS exposure) subjects with cotinine above 100 ng/mg creatinine were excluded from the group of nonsmokers. In the Fontham study (which only used cotinine to corroborate current smoking status and not to assess ETS exposure) an identical exclusion criterion was used. It should be noted that, in the Fontham study, where the urine sample was taken on cases who already had lung cancer, the cotinine measurement would not detect past smoking (other than in the previous few days). Many patients give up smoking around the time of lung cancer diagnosis.

3.9 Data on potential confounding variables

The studies collected a variable amount of information on potential confounding variables. A summary of how these data were taken into account in the analysis is presented in Appendix C.

3.10 Weaknesses of the studies

As can be seen from Appendices E and F, all the larger studies have weaknesses in design or analysis which affect the interpretation of their findings. While the faults vary from study to study, a number are relatively common, including:

(i) small number of cases;

(ii) failure to insist on histological confirmation of cases;

(iii) use of surrogate respondents for a large proportion of subjects;

(iv) use of a higher proportion of surrogate respondents in cases than in controls;

(v) interviewing of cases and controls in differing situations;

(vi) selection of controls using a procedure which makes them unrepresentative of, or not comparable to, the cases;

(vii) failure to determine ETS exposure objectively;

(viii) failure to confirm smoking status adequately;

(ix) failure to collect adequate data on potential confounding variables;

(x) failure during analysis to adjust for potential confounding variables for which data have been collected;

(xi) failure, in prospective studies, to follow-up all subjects;

(xii) limited reporting of results and of study design details;

(xiii) overemphasis on occasional significant findings, without properly considering the effects of the multiple statistical tests carried out;

(xiv) failure to restrict attention to married subjects when studying effects of spousal ETS exposure and to working subjects when studying effects of workplace ETS exposure; and

(xv) failure to adjust adequately for age.

4. Smoking by the husband

4.1 Introduction

Table 2 summarizes data from the 44 studies that provide relevant data. For eight of the studies (see Table 14), the index of exposure is not actually based on husband's smoking directly, but on the nearest equivalent index. Table 2 shows relative risks and 95% CIs for each study, both unadjusted and adjusted for covariates, with significant ($p<0.05$) positive or negative relative risks indicated by a + or - sign respectively.

Results of various meta-analyses of these data are shown in Table 3, combined relative risk estimates being presented for all 44 studies and for various subgroups of studies, subdivided according to different study characteristics. The covariate adjusted meta-analyses are based on covariate adjusted data, if available for a study, and on unadjusted data, if not. Similarly covariate adjusted data are used in the unadjusted meta-analyses, if unadjusted data are not available.

4.2 Overall association

Based on the overall data for lifelong nonsmoking women, the relative risk associated with smoking by the husband is estimated using fixed-effects meta-analysis as 1.19 (95% CI 1.11-1.28) for the unadjusted data and 1.16 (95% CI 1.09-1.25) for the covariate adjusted data. There is evidence of significant heterogeneity between the individual study estimates ($p<0.05$ unadjusted, $p<0.001$ adjusted). One method of attempting to take account of this is to use random-effects meta-analysis, which considers variation between study as well as within study. Using the Hardy and Thompson method [67] this gives somewhat higher estimates, 1.23 (95% CI 1.12-1.36) for the unadjusted data and 1.24 (95% CI 1.12-1.39) for the covariate adjusted data. However, such random-effects estimates are open to question [66] and it is more helpful to look at variation in relative risk according to various study characteristics in order to try to explain the heterogeneity between the individual estimates. Results summarized in Table 3 for various study characteristics are considered in the sections that follow, relative risks and CIs cited and conclusions drawn being based on the covariate-adjusted data and on fixed-effects meta-analyses.

4.3 Geographical inconsistency

Although the relative risk estimates are significant for studies conducted in the USA (1.12, 95% CI 1.01-1.24), in Europe (1.62, 95% CI 1.29-2.04) and in Asia (1.13, 95% CI 1.02-1.26), the higher estimate in Europe means that there is significant ($p<0.05$) variation between continent. Within Asia there is also significant ($p<0.05$) variation between country, with the relative risk significant for Japan (1.30, 95% CI 1.05-1.60) and Hong Kong (1.45, 95% CI 1.13-1.86) but not for China/Korea (1.00, 95% CI 0.87-1.14). Even within China/Korea significant ($p<0.001$) heterogeneity is evident, the significant positive relative risks shown in Table 2 for the Geng and Wang S-Y studies contrasting with the significant negative relative risk for the Wu-Williams study and the general lack of evidence of an association seen in the other seven Chinese and Korean studies.

4.4 Inconsistency over time

There is evidence of highly significant ($p<0.001$) heterogeneity over time, with the relative risk estimates significant for the 25 studies published in the 1980s (1.36, 95% CI 1.22-1.52) but not significant for the 19 studies published in the 1990s (1.06, 95% CI 0.97-1.16). This explains why the overall relative risk estimate of 1.16 for the 44 studies is considerably less than earlier estimates, e.g. by Wald and the US National Research Council [49,50], or for those studies referred to in the Independent Scientific Committee on Smoking and Health (ISCSH) Third and Fourth Reports in 1983 and 1988 [52,68].

4.5 Inconsistency across study size

In the 15 studies involving over 100 lung cancer cases the overall association is only marginally significant (relative risk 1.09, 95% CI 1.01-1.19) and weaker than seen in the 15 studies of 50-100 cases (1.43, 95% CI 1.22-1.67), and the 14 studies of less than 50 cases (1.24, 95% CI 0.95-1.62). This significant ($p<0.05$) heterogeneity of relative risk by study size may reflect a possible failure to publish negative results from small studies.

4.6 Inconsistency across study quality

There are many possible ways of attempting to define study quality. In one approach [69], studies have been defined as "superior" only if they had none of the following deficiencies: (i) less than 10 lung cancer cases, (ii) cases and controls from different hospitals, (iii) cases and controls interviewed in different places, (iv) all respondents next-of kin, (v) substantially more case than control interviews by next-of-kin respondents, (vi) controls and cases unmatched on vital status, and (vii) no details provided on controls. Based on this definition of study quality, meta-analysis showed some evidence of a difference in relative risk between the 23 "superior" studies (1.10, 95% CI 1.00-1.21) and the 21 "inferior" studies (1.24, 95% CI 1.12-1.38). This difference was not quite significant ($0.05 < p < 0.1$).

4.7 Inconsistency across study type

Although there was no significant difference between the relative risk estimates for the five prospective studies (1.23, 95% CI 1.03-1.48) and the 39 case-control studies (1.15, 95% CI 1.07-1.24), there was evidence of significant ($p<0.05$) variation by more detailed study type, with an association evident for case-control studies using "diseased" (hospital or decedent) controls (1.34, 95% CI 1.18-1.53), but not for case-control studies using "healthy" (population) controls (1.06, 95% CI 0.97-1.16).

4.8 Confounding

Recent studies [70,71] have clearly demonstrated that, among nonsmokers, living with a smoker is associated with increased exposure to a wide range of risk factors for lung cancer. Among other things, living with a smoker is associated with increased exposure to occupational risk factors and with a poorer diet, higher in dietary fat and lower in antioxidants. These studies support earlier suggestions [54] that confounding may explain some or all of the increased risk of lung cancer associated with smoking by the husband. As is made clear in Appendix C (which considers also the two studies not providing data on spousal smoking) the adequacy of risk factor adjustment in the 46 studies was limited.

It can be seen from Appendix C that:

(a) About a quarter (12/46) of the studies failed to adjust for age. In a number of these studies, the lifelong nonsmoking cases and controls used in the ETS analyses had been selected from an original set of subjects which also included current and former smokers. While the researchers had taken care to ensure the original set of cases and controls were age-matched, they had not taken any steps to ensure that the selected lifelong nonsmoking cases and controls would be.

(b) About two-thirds (22/36) of the studies using smoking by the husband as an index of ETS exposure failed to restrict analyses to married women. As the exposed group are all, by definition, married but the unexposed group contains a mixture of married and unmarried women, there is an inevitable confounding between possible effects of marital status (and its correlates) and of ETS exposure.

(c) Over a third (17/46) of the studies took no other potential confounding factors into account. Known risk factors for lung cancer were adjusted for in very few studies, e.g. occupation in only six studies and diet in only three studies.

As shown in Table 3, relative risk estimates for husband's smoking were highly significantly ($p<0.001$) higher in the 16 studies that had taken no confounding variables at all (other than possibly age or marital status) into account (1.46, 95% CI 1.27-1.69) than in the other 28 studies (1.08, 95% CI 1.00-1.17).

4.9 Histological type

Lung cancer is not a single disease. There are a number of different histological types, the two most common being squamous cell carcinoma and adenocarcinoma. These types have different aetiologies and risk factors, cigarette smoking being much less associated with adenocarcinoma [72,73] than with squamous cell carcinoma.

Some have reasoned that ETS is a cause of lung cancer by analogy to active smoking. If ETS were in fact a cause of lung cancer in nonsmokers due to its claimed similarity to mainstream smoke, the same pattern of increased risk for specific histological types might then be expected. Sixteen of the epidemiological studies separate results relating to smoking by the husband by histological type. Although these studies vary in the way types are combined, it is possible to compare results for two main

groups, one including adenocarcinoma and the other including squamous call carcinoma (Table 4). These data do not clearly support the above expectation. While some studies present results seemingly more consistent with an association with squamous cell carcinoma than with adenocarcinoma, other studies present results suggesting an association with adenocarcinoma.

For 19 of the studies lung cancer diagnosis was confirmed in all the cases by histology. In the other 25 studies a proportion, often substantial, of diagnoses were based on less reliable methods such as X-ray or cytology. There was a tendency for the relative risk to be higher in the former group (1.28, 95% CI 1.15-1.43) than in the latter group (1.09, 95% CI 1.00-1.19), the difference between the two estimates being statistically significant ($p<0.05$). It should be noted that clinical diagnosis of lung cancer involves substantial errors, with 10-20% or more of cases diagnosed clinically not confirmed at autopsy [74]. Even where histological "confirmation" is available, there is a danger that cases diagnosed as having primary lung cancer may in fact have metastases of tumours of other sites [75].

4.10 Dose-response

Twenty-eight of the spousal studies have reported one or more kinds of dose-response data. Nineteen studies have reported risk in relation to the number of cigarettes per day smoked by the husband, 16 studies have reported risk in relation to the number of years of exposure to smoking from the husband, and five studies have reported risk in relation to the number of pack-years of exposure from the husband. The results for these three measurements of dose are summarized in Tables 5, 6 and 7, respectively.

Tables 5-7 include the results of two tests of significance of linear trend. Although many studies only report the results of trend tests including the unexposed group, Breslow and Day [76] have suggested that trend tests excluding the unexposed group may be more appropriate because tests including the unexposed group "may sometimes give a significant result even if the relative risks are not continuously increasing". Appendix G gives details of how the significance of the trend statistics was calculated from the often limited data in the individual studies.

Together, Tables 5 to 7 present 40 dose-response data sets. The overall data clearly provide some evidence of a dose-response relationship. Thus, there are 34 data sets where the risk in the highest exposed group exceeded that in the unexposed group, a number higher than the 20 expected by chance. Furthermore there are 10 significant positive trends including the unexposed group and 5 significant positive trends excluding the unexposed group, as against no significant negative trends calculated either way.

However, it was notable that none of the 40 data sets showed a monotonic dose-response relationship with the trend significant both including and excluding the unexposed group. Some of the significant trends included studies (e.g. Lam T, see Table 5) where exposed groups had an elevated risk generally, but there was no evidence of any increase with increasing exposure, and studies (e.g. Brownson 2, see Table 7) where the relative risk estimate was increased at high exposure and decreased at low exposure.

It was also notable (see Table 3) that the overall relative risk associated with smoking by the husband was highly significant ($p<0.001$) for those studies reporting dose-response data (1.24, 95% CI 1.14-1.35) but was not significantly elevated for those studies not reporting dose-response data (1.02, 95% CI 0.90-1.15). This indicates that the studies presenting dose-response data are unrepresentative of all studies reported. Other sources of potential bias to the dose-response data are discussed in section 13.9.

4.11 Misclassification of active smoking status

As clearly demonstrated in a recent literature review by Lee and Forey [64], there is abundant evidence that a proportion of current or former smokers deny ever having smoked (or are reported by proxy respondents as never having smoked) and are falsely categorized as lifelong nonsmokers. Denial of smoking may arise for a number of reasons, including not wanting to admit having ignored medical advice to give up smoking, not wanting to admit a socially unacceptable habit (e.g. smoking by women in Japan), not wanting to risk invalidating a nonsmoking life insurance policy, failure to remember past smoking, not wanting to have to answer further detailed questions in a long and boring questionnaire, and wrongly assuming the questioner is uninterested in

cigarettes smoked many years ago or in a small number of cigarettes smoked now [64]. There is also the possibility of a clerical error in data entry or subsequent processing.

It has been known for a number of years [49,50,77] that inclusion of even just a few misclassified smokers among the lifelong nonsmokers will, because of the tendency for husbands and wives to share smoking habits more often than expected by chance, lead to a higher risk of lung cancer in reported lifelong nonsmokers married to smokers, even in the absence of any true effect of ETS exposure. Although the EPA [53] attempted to correct for bias due to misclassification of active smoking status, the data presented so far in Tables 2 to 7 relating lung cancer risk to husband's smoking have not been so corrected. One reason for this is evidence that misclassification rates vary quite widely according to the situation in which the questions are asked [78], so making it unreliable to assume that any specific misclassification rate is necessarily appropriate to apply in all situations. Also, as discussed below, there is evidence that misclassification rates vary by country, and data are limited or non-existent for some countries.

Despite these reservations, we present the results of an attempt to illustrate the effect of misclassification on relative risks associated with smoking by the husband. The methodology used is that recently described by Lee and Forey [63]. In order to carry out the correction, one has to specify:

(i) **Misclassification rates**. Lee and Forey [63,64] concluded that in the *USA* an estimate of 2.5% for the misclassification rate of ever smokers as never smokers would probably be most appropriate, though an appropriate figure could, not

implausibly, be anywhere in the range 1 to 4%[★]. 1%, 2.5% and 4% have been used for illustrative purposes in the analyses. There is also evidence [79,80] that misclassification rates may be much higher in *Asia* than in the USA. Some results have been included based on rates of 5%, 10% and 20%, though the data from one study [80] suggests even higher rates than this. Lee and Forey did not discuss the more limited data for *Europe*. Values of 1%, 2.5% and 4% have been used, as in the USA. However, it is possible that rates may be higher than this in some parts of Europe. As there is no evidence on smoking habit misclassification in Greece or Russia, some of the misclassification analyses presented exclude results from the three studies conducted in these countries [4,27,39], which in fact contribute to a large extent to the elevated relative risk estimate in Europe.

(ii) **Concordance ratios**.[★★] Following Lee and Forey [63], a central estimate of 3.0 has been used, with some results given for alternative estimates of 2.0 and 4.0.

[★] Note that the 2.5% misclassification rate cited (and also the other rates) refers to ever smokers of average lung cancer risk, i.e. the bias to be expected would be the same as if all ever smokers had the same risk and 2.5% denied smoking. The probability that an ex-smoker will report never having smoked is actually substantially greater than this, but ex-smokers who deny smoking have relatively low risk. Lee and Forey [63] justify use of these rates in detail.

[★★]The concordance ratio, or aggregation factor, measures the tendency for husbands and wives to share smoking habits more than expected by chance. It is equal to the odds, for a smoker, of being married to a smoker, divided by the corresponding odds for a nonsmoker.

(iii) **Models**. Results are mainly shown using the multiplicative model for the joint association of active smoking and ETS with lung cancer risk but some results are also shown for the additive model. Choice of model in fact had little effect.

Table 8 shows the main results of the misclassification-corrected analyses. This table shows the meta-analysis relative-risk estimates (and 95% CIs) for the three continents separately and together for five sets of assumptions:

a) Assuming no misclassification;

b) Assuming a concordance ratio of 3.0, a multiplicative model and "lower" levels of misclassification (1, 2.5, 4%) in all continents;

c) Assuming a concordance ratio of 3.0, a multiplicative model, a 2.5% misclassification rate in USA and Europe but allowing for "higher" levels of misclassification (5, 10, 20%) in Asia;

d) Assuming a misclassification rate of 2.5% in all continents, but varying the concordance ratio and/or the model;

e) Assuming a misclassification rate of 2.5% in USA and Europe but 10% in Asia and again varying the concordance ratio and/or the model.

Results are presented with and without the studies conducted in Greece and Russia. The non-misclassified and the main misclassification-corrected estimates are shown in bold face in Table 8. For further illustration of the effects of misclassification, Table 9 shows the effect of various rates of misclassification on the individual relative risks for those studies with over 100 lung cancer cases. In this table a concordance ratio of 3.0 and a multiplicative model was assumed.

Table 8 shows that correction assuming a 2.5% misclassification rate would essentially eliminate the weak association between husband's smoking and lung cancer in the USA (relative risk 1.01, 95% CI 0.90-1.12 for a concordance of 3.0) and even a lesser rate would render the association clearly nonsignificant. While correction using a 2.5% misclassification rate would have little effect in Asia, using a 10% rate would render the relative risk only marginally significant (1.12, 95% CI 1.00-1.25) and a 20% rate would virtually eliminate the association completely (1.02, 95% CI 0.90-1.14). Correction using a 2.5% misclassification rate would also reduce somewhat the relative

risk estimates for Europe. Excluding studies in Greece and Russia, countries where we have no data on misclassification rates, the misclassification-corrected estimate for Europe would not be significant (1.12, 95% CI 0.77-1.63).

Overall, if one conservatively assumes a 2.5% misclassification rate in the USA and Europe and a 10% misclassification rate in Asia, and retains the Greek and Russian studies, the overall meta-analysis relative risk based on 44 studies reduces from an unadjusted 1.19 (95% CI 1.11-1.28) to a corrected 1.10 (95% CI 1.02-1.18). Using instead a rate of 20% in Asia would reduce it further, to a nonsignificant 1.05 (95% CI 0.98-1.14). Again assuming a 2.5% misclassification rate in the USA and Europe and a 10% misclassification rate in Asia, but this time excluding the Greek and Russian studies, the overall meta-analysis relative risk, now based on 41 studies, reduces from an unadjusted 1.16 (95% CI 1.08-1.25) to a corrected 1.06 (95% CI 0.99-1.15). Here using a rate of 20% in Asia reduces the estimate to 1.01 (95% CI 0.94-1.10).

The reduction in relative risk caused by misclassification correction is somewhat greater assuming a concordance ratio of 4.0 and somewhat less assuming a concordance ratio of 2.0, but the conclusion that correction for misclassification has a marked effect on the overall association is unchanged.

It is not technically possible formally to correct for misclassification **and** adjust for confounding in the same analysis. However, as adjustment for confounders reduced the non-misclassification-corrected meta-analysis relative risk estimates from 1.19 to 1.16 (see Table 3), i.e. down by 0.03, it might be expected it would also reduce the misclassification-corrected estimates down by about 0.03. If so, then assuming a misclassification rate of 2.5% for USA and Europe and of 10% for Asia, and including the Greek and Russian studies, the misclassification-corrected relative risk of 1.10 (95% CI 1.02-1.18) would reduce to about 1.07 (95% CI 0.99-1.15). Excluding the Greek and Russian studies, the misclassification corrected estimate of 1.06 (95% CI 0.99-1.15) would reduce to about 1.03 (95% CI 0.97-1.12).

It is certainly plausible that misclassification, coupled with confounding, could

explain essentially all the apparent association between husband's smoking and lung cancer.

4.12 Other aspects of smoking by the husband

Some studies provide results for more than one index of smoking by the husband. Where there is a choice in Table 2 the data presented relate to the index nearest to "husband ever smoked", as this is the index most commonly used in the studies. Data relating to these other indices is given in Table H1 of Appendix H. For six of the seven studies cited, no significant relationships were reported, and for the other (Garfinkel 2) study, the significant relationship reported (for husband's cigarettes smoked at home) is similar to that given in Table 5 (for husband's total smoking habits). These additional data, therefore, add little to support an association between ETS and lung cancer.

4.13 Sources of variation in relative risk estimates for smoking by the husband

Earlier in Section 4, based on analyses summarized in Table 3, it has been shown that various factors are separately significantly associated with the relative risk for smoking by the husband. These factors are not all independent. In Appendix I results of some multiple regression analyses simultaneously considering these factors are presented. While they do not clearly identify specific factors responsible for the heterogeneity of risk, they do show that more than one factor is involved and that the variation in risk associated with independent factors is greater than the overall risk associated with marriage to a smoking husband.

5. Smoking by the wife

Nonsmoking men married to smoking women are much less common (especially in Asia) than nonsmoking women married to smoking men. As a consequence, the data in relation to smoking by the wife, summarized in Table 10, are rather sparse, being based on only 15 studies and less than 500 lung cancer cases. Although a significant ($p<0.05$) relative risk was reported in the Hirayama study, no significant relative risks were seen in any other study, including that by Cardenas, which involves the most cases.

Because of this, meta-analysis of the overall data (Table 11) did not show a significant relative risk associated with wife's smoking (1.24, 95% CI 0.98-1.57 adjusted for covariates). Although this association is almost statistically significant, it is subject to the same types of bias referred to in Section 4 in relation to smoking by the husband.

Table 12 presents limited data relating to extent of exposure to smoking from the wife. Considered overall there was no evidence of a dose-response relationship. Some additional data, shown in Table H1 of Appendix H, relating to other indices of exposure from the wife, do not show any significant relationships.

6. Smoking by the spouse

Table 13 presents results of various meta-analyses of the data for smoking by the spouse, based on the combined evidence for smoking by the husband in Table 2 and for smoking by the wife in Table 10. The relative risks and 95% CIs shown are very similar to those given in Table 3 for smoking by the husband, reflecting the fact that a very large proportion of the total data on spousal smoking relates to smoking by the husband.

7. Smoking in the household

While smoking by the husband is the most commonly used index of ETS exposure at home, many of the studies provide data on risk of lung cancer in lifelong nonsmoking women in relation to other indices of ETS exposure at home without specific reference to the husband.

Table 14 presents data for women from 22 studies. For eight of these studies the data presented have already been included in Table 2. For the remaining 14 studies, Table 14 presents new data, including relative risk estimates for multiple indices of exposure. Although four of the studies do report a statistically significant increase in risk in relation to one or more such indices, the data overall do not provide any real evidence of an association, with 12 of the 33 relative risks being less than 1.0.

The lack of clear association with household exposure is further illustrated by the data from eight studies shown in Table 15 relating to extent of ETS exposure in the household. Of 12 trend tests for women and three for men (see footnotes to the table) only one was reported to be significant, and that was in a study [43] where the data were inadequately reported.

Of all the indices of household exposure to ETS, the only one to show any clear association with lung cancer risk is "smoking by the husband." This view is supported by meta-analysis results in Table 3 showing that the covariate-adjusted relative risk is significant ($p<0.001$) for the 36 studies specifically using husband's smoking as the index (1.17, 95% CI 1.09-1.25) but not for the eight studies using other indices, based on more general ETS exposure (1.11, 95% CI 0.86-1.43).

8. Smoking in the workplace

Table 16 summarizes data from 18 studies. Statistically significant positive relationships were only reported in the Kabat 1 study for males and in the Fontham study for females. A meta-analysis of the relative risks in Table 16 (see Table 25) gives a combined estimate of 1.03 (95% CI 0.95-1.11) for unadjusted data and of 1.05 (95% CI 0.96-1.14) for covariate adjusted data, suggesting no association of workplace ETS exposure with risk of lung cancer. These analyses, which did not demonstrate any significant between-study heterogeneity, did not include data from the Stockwell study, which reported finding no association, but gave no detailed results, or from the Cardenas study, which only reported risk by level of exposure, finding no association either.

The absence of an association of lung cancer with workplace ETS exposure is further demonstrated in Table 17, which concerns extent of exposure. Apart from for the Fontham study, where an association with overall workplace exposure has already been noted, the results for none of the other four studies suggest any association with extent of ETS exposure. As regards the Fontham study, it should be noted that the relative risks shown in Table 16 are only significant for the covariate adjusted data, with adjustment, unusually and inexplicably, substantially increasing the relative risk from 1.12 (95% CI 0.91-1.36) to 1.39 (95% CI 1.11-1.74).

9. ETS exposure in childhood

Table 18 summarizes data from 18 studies. Only two statistically significant relative risks were reported, an increased risk in the Sun study for females and a decreased risk in the Brownson 2 study for females. A meta-analysis of the relative risks in Table 18 (see Table 25) gives a combined estimate of 0.99 (95% CI 0.90-1.08) for unadjusted data and of 1.01 (95% CI 0.92-1.11) for covariate adjusted data, suggesting no association of childhood ETS exposure with risk of lung cancer. These analyses, which demonstrated significant ($p<0.01$) between-study heterogeneity, did not include data from the Akiba and Correa studies, which reported finding no association, but gave no detailed results.

The relative risks in Table 18 are based on any household exposure, if available, or smoking by the mother if not. Some studies presented data on more than one index of exposure, but their results (see Table H2 in Appendix H) did not alter the overall evidence of a lack of association with childhood ETS exposure.

Table 19 presents data relating to extent of ETS exposure in childhood. Results are shown for eight dose-response relationships for women and (in the footnotes) for two for men. The findings are rather variable, with results from four studies showing no increase at all in ETS exposed subjects, but results for three showing a statistically significant ($p<0.05$) positive trend. It should be pointed out that, for two of the three positive trends, in the Brownson 2 and Kabat 2 studies, the index of exposure used seemed rather subjective and might have been affected by recall bias. In both these studies other indices of childhood exposure did not show any trend, suggesting that this explanation is a plausible one.

Overall the data do not demonstrate that childhood ETS exposure affects risk of lung cancer.

10. Social exposure to ETS

Table 20 summarizes data from six studies. While a significant ($p<0.05$) positive relationship was seen in the Fontham study for females, a significant negative relationship was seen in the Janerich study for the sexes combined. A meta-analysis of the relative risks in Table 20 (see Table 25) gave a combined estimate of 1.09 (95% CI 0.94-1.28) for unadjusted data and 1.10 (95% CI 0.94-1.30) for adjusted data, suggesting no association of social ETS exposure with risk of lung cancer. These analyses, which demonstrated highly significant ($p<0.001$) heterogeneity, did not include data from the Stockwell study, which reported finding no association, but gave no detailed results.

The lack of association of lung cancer with social ETS exposure is further shown in Table 21, which concerns extent of exposure. The positive trend in the Fontham study reflects the association noted in Table 20, with no other study reporting a significant positive trend, and one, Lee, reporting a significant ($p<0.05$) negative trend.

11. Total ETS exposure

A number of studies have presented additional data relating to ETS exposure from more than one source and/or time period. Relative risks and 95% CIs from these studies are presented in Tables 22 and 23. Included in the tables are results from the de Waard study, which related risks to a single urinary cotinine measurement, and from the Shen study, which related risk to "exposure to ETS of >20 cigarettes/day" (source and time period unspecified), the only two studies whose results cannot be included in the data in Table 2 on husband's smoking. Not included in the tables are results already reported, e.g. in Table 14. As can be seen, the various indices of exposure used are very disparate, and cannot meaningfully be combined by meta-analysis. The overall impression from these data is that an association has not been consistently demonstrated, and that they add little to the data for the more specific exposure indices already considered in Tables 2, 10, 16, 18 and 20. The results are, of course, subject to similar biases to those noted above for husband's smoking, especially since husband's smoking would have contributed to all the various indices of exposure considered.

12. Multiple sources of ETS exposure

The great majority of results presented in the 44 epidemiological studies relate to single indices of ETS exposure, ignoring other indices. For example, a study may compare subjects exposed or not exposed to spousal smoking, exposed or not exposed to workplace ETS exposure, and exposed or not exposed to childhood ETS exposure. Especially since such indices may be correlated, and since it might be considered desirable to make comparisons with a completely unexposed group, it might seem preferable to compare risks in subjects classified jointly by the various sources of exposure. Thus with data on two sources available, one would compare subjects exposed to both, or to either one but not the other, with subjects exposed to neither. In fact, such analyses have very rarely been attempted, partly because limited numbers of cases would mean small numbers in each category of exposure except in the largest studies. Generally such analyses, where they have been conducted, have not suggested any interaction between multiple sources of exposure. In the case of the Koo study, where results were presented relating to the joint effect of childhood and adulthood exposure and of at home and workplace exposure, numbers of women exposed in childhood and at work were too small for useful results. In the case of the Svensson study, where similar analyses were performed, the same conclusion can be reached. In a much larger study (Brownson 2) risk was examined jointly in relation to childhood and adulthood exposure. No results were presented, but it was noted that "there was no evidence of interaction between exposure during the two periods."

In the largest study so far conducted (Fontham), some evidence of an interaction was noted. Based on data summarized in Table 24 the authors concluded that "women who were exposed during childhood had higher RRs associated with adult-life ETS exposures than women with no childhood exposure." As is shown in Table 24, this conclusion seems somewhat misleading, being based on a comparison of relative risks for adult exposure separately computed for those women who were or were not exposed in childhood. If the risks are all computed relative to the **same** base, women who are unexposed in both childhood and adulthood, a different pattern emerges, with risk **reduced** in women exposed in childhood only and not increased in women exposed in adulthood, regardless of their childhood exposure. The data actually provided by

Fontham (in her Table 8) give risk by level of adulthood exposure in smoke-years. Fitting a linear logistic model to these data actually shows no evidence of an effect of childhood ETS exposure nor of any interaction between childhood and adulthood ETS exposure. There is a significant ($p<0.01$) trend with smoke-years adult ETS exposure, but this may result from some of the sources of bias referred to earlier, including misclassification of smoking status and recall bias.

The data on multiple sources of ETS exposure add little to the overall picture.

13. Interpretation

13.1 Association between lung cancer and ETS specific to spousal smoking

Table 25 summarizes results of unadjusted and covariate adjusted meta-analyses for the five main indices of ETS exposure considered in Sections 4 to 12. There is little or no evidence of an association between lung cancer and workplace exposure, based on 18 studies, childhood exposure, based on 18 studies, or social exposure, based on 6 studies. There is, however, some evidence of an association of lung cancer with spousal smoking. The association is highly significant ($p<0.001$) for husband's smoking, where the covariate adjusted relative risk is 1.16 (95% CI 1.09-1.25), based on 44 studies. The association with wife's smoking has a higher relative risk estimate, 1.24, but is not significant at the 95% confidence level (95% CI 0.98-1.57), being based on 15 studies and about 10 times fewer deaths than for husband's smoking.

The evidence would seem to indicate that any association with lung cancer that might exist is with spousal smoking. This view is supported by noting that no significant overall association was evident for those eight studies included in Table 2 under husband's smoking which in fact used a less specific index of exposure such as exposed at home or at work (see Table 8). It is not affected by consideration of the results for more general indices of household exposure (Table 14) or for total exposure (Table 20) which showed less clear evidence of an association than was the case for spousal smoking, despite the fact that smoking by the spouse would have contributed to the index of exposure used for most of the relationships considered.

The question arises as to whether the weak association with spousal smoking indicates a causal relationship between lung cancer and ETS exposure.

13.2 Validity of spousal smoking as a marker of ETS exposure

A limitation of the studies considered in this review is that, with only one exception, indices of ETS exposure have been derived from questionnaire responses rather than from attempts to measure exposure using ambient air concentrations of tobacco smoke constituents or of uptake of constituents in body fluids. Even the exception, a study in Holland [41] in which urinary cotinine levels in nonsmokers were

related to subsequent lung cancer risk, was based on too few deaths to provide useful results.

There is evidence from a number of studies in US and Western European populations that cotinine levels in nonsmokers are increased in relation to smoking by the husband or self-reported indices of ETS exposure at home [77,81-86]. However a recent study of 400 women in Japan [79], which reported nonsignificantly **lower** urinary cotinine in nonsmokers married to smokers than in nonsmokers married to nonsmokers suggests that one cannot necessarily assume that spousal smoking is a valid marker of increased ETS exposure in all populations. More evidence is needed here, partly to resolve the apparent conflict with the results of a study conducted in 13 centres in Asia, Europe and the USA [87] which reported that urinary cotinine was significantly positively associated with various indices of ETS exposure, and partly as evidence from ETS biomarker studies is virtually or completely nonexistent for China, Hong Kong, Greece and Russia, all countries where significant relationships have been observed between lung cancer and spousal smoking.

Whatever the merits of differing questionnaire indices of ETS exposure, it is inevitable that there will be errors in the data collected. Random errors will lead to a tendency to underestimate any true relationship of ETS to lung cancer risk; but differential errors can cause bias in either direction. The possibility of recall bias, with cases with lung cancer being more likely than controls to have a higher ratio of reported to true ETS exposure, is discussed further in Section 13.6.

13.3 Plausibility

There is evidence from a number of studies that cotinine levels are more strongly associated with marriage to a smoker than with working with a smoker [81,86,87], though another study did not report this [83]. Some might argue, therefore, that the reason an association with lung cancer is evident for spousal smoking but not for other indices of ETS exposure is because spousal smoking is a better marker than other indices. Even ignoring the inconsistency of the cotinine evidence [79,83], there are a number of reasons why this interpretation can be questioned.

First, it would seem implausible that marriage to a smoker would be associated with as high a relative risk of lung cancer as 1.16, given the very low exposure to smoke constituents associated with marriage to a smoker. A recent study in Yorkshire, in which nonsmoking subjects wore a personal air sampler for 24 hours [88], estimated that having a smoking partner was associated with an increased median ETS exposure of 131 mg of particles and 19.4 mg of nicotine in a **year**. The annual exposures are, respectively, 0.15% and 0.27% of those of a typical smoker of 20 cigarettes a **day** delivering 12 mg of particles and 1 mg of nicotine per cigarette. Assuming that average smokers smoke 20 cigarettes a day, that active smoking is associated with an eight-fold increase in risk of lung cancer,★ and that risk is linearly related to exposure, one would predict a relative risk associated with marriage to a smoker of 1.01, based on particles, or 1.02, based on nicotine. Bearing in mind that there is evidence that in smokers the dose-response relationship may have a quadratic component [91], thus predicting an even smaller risk associated with ETS exposure, and also the possibility of a threshold, this suggests that it is rather unlikely that an increased relative risk as high as 1.16 associated with having a smoking husband could have arisen as a result of ETS exposure.

Second, the epidemiological studies of ETS and lung cancer are open to a number of sources of bias, some of which are more relevant to relative risk estimates based on spousal smoking than to those based on other indices, such as childhood or workplace ETS exposure. These sources of bias, which have been referred to already, particularly in Section 4, are discussed further in the sections that follow.

★Approximate relative risk estimate for ever/never smokers based on the British Doctors' study [89] and the American Cancer Society Cancer Prevention Studies I and II [90].

13.4 Misclassification bias

As noted in Section 4.11, recent publications have quantified the extent to which current and former smokers deny smoking [64] and have clarified the statistical methodology by which spousal smoking/lung cancer relative risk estimates should be corrected to take account of bias arising from misclassification of active smoking status [63]. These publications concluded that, for US or Western European studies, the bias is similar to that calculated assuming about 2.5% of average risk ever smokers are misclassified as never smokers. However, considerable uncertainties were noted and it was suggested that an appropriate figure is "probably in the range 2-3 per cent but ... not implausibly ... anywhere in the range 1-4 per cent" [63].

Using a 2.5% misclassification rate to correct the unadjusted USA relative risk of 1.12 (95% CI 1.01-1.24) would virtually eliminate the association completely, reducing it to 1.01 (95% CI 0.90-1.12), and even assuming a rate of 1.0% would render it nonsignificant. It is clear that misclassification can explain most, if not all, of the association with spousal smoking evident in the USA.

Correcting the unadjusted Asian relative risk of 1.20 (95% CI 1.09-1.34), using a 2.5% misclassification rate would only reduce it to 1.18 (95% CI 1.06-1.32), so having relatively little effect. However two recent studies have suggested that misclassification rates in Asian women may be very much higher than 2.5%. One study [79] reported that as many as **20.8%** married Japanese current smokers (as determined by cotinine) claimed to be never smokers, with the misclassified smokers having very similar cotinine levels to the smokers who admitted smoking. The other study [80] presented results indicating that as many as **62%** of Cambodian, Laotian and Vietnamese women living in Ohio who were current smokers (again as determined by cotinine) denied smoking, with cotinine values for the deniers "well within the active smoking range." While the evidence is still limited, and need not necessarily be fully applicable to studies in China, Hong Kong or Korea or to the situation pertaining in studies conducted many years ago, such as Hirayama's [6], it certainly seems appropriate to use a much higher misclassification rate when correcting relative risks for Asian women. As shown in Table 8, assuming a 20% rate essentially eliminates the association, reducing it to 1.02 (95% CI 0.90-1.14) while

even a 10% rate would render it nonsignificant.

For the European data, where the unadjusted data give a relative risk of 1.52 (95% CI 1.22-1.90), correction using a 2.5% misclassification rate would only reduce it slightly, to 1.48 (95% CI 1.18-1.86). It should be noted that the three studies which contribute most to the overall association in Europe were not carried out in Western Europe, from where much of the evidence on misclassification rates comes, but from Greece [4,27] and Russia [39], where no such evidence is available. If, however, one were to assume, somewhat speculatively, a 20% misclassification rate for Greece and Russia and a 2.5% rate for Western Europe, the relative risk would only reduce to 1.39 (95% CI 1.10-1.75) and stay statistically significant.

The misclassification-corrected rates cited above assume a between-spouse smoking habit concordance ratio of 3.0 and a multiplicative model. Using reasonable alternative assumptions would not affect the general conclusion that bias due to misclassification of active smoking status is an important determinant of the association reported between lung cancer and smoking by the husband.

One study, Fontham [36], in an attempt to control for misclassification bias, excluded subjects with cotinine levels in urine that were typical of smokers. Although this study reported a significant association with spousal smoking, this does not affect our conclusion that misclassification bias is important. As noted by the European Working Group [60], Fontham's approach to misclassification was inadequate. The half-life of cotinine in urine is relatively short, and the cotinine checks would be inadequate to detect those lung cancer cases who gave up smoking around the time of diagnosis and before the urine sample was collected. Since recent giving up would be much less common in controls, the effect of Fontham's use of cotinine would be to eliminate a greater proportion of the misclassified smokers in the controls than in the cases, so exacerbating rather than reducing any bias due to misclassification.

13.5 Confounding

Confounding is likely to be particularly relevant in epidemiological studies in

which there is a weak association between the exposure and the disease of interest, the association varies between countries and across studies, there are numerous other risk factors for the disease that are correlated with exposure, those risk factors for which data have been collected are subject to error, and there are risk factors for which data have not been collected.

All these points apply to the association between ETS exposure, as indexed by spousal smoking, and lung cancer. Elaborating further, one should note:

(a) There are a large number of risk factors for lung cancer, including family history of lung cancer and of tuberculosis, personal history of various lung diseases, hormonal factors, keeping pet birds, a variety of cooking methods, various occupations, motor exhaust, physical inactivity, and a number of aspects of diet [92].

(b) Analyses based on data from the UK Health and Lifestyle Survey [70] have shown that a wide range of lifestyle factors commonly associated with adverse health are more common in smokers than in nonsmokers and also in nonsmokers living with a smoker, and have led to the conclusion that the magnitude of bias from confounding by multiple risk factors may be important where weak associations are observed.

(c) The importance of confounding in epidemiological studies of ETS is further emphasized by, as yet unpublished, analyses of follow-up data from the same survey [93]. These analyses showed that, within nonsmokers, salivary cotinine is even more strongly associated with risk factor prevalence than is living with a smoker, the marker of ETS exposure previously used. Of 31 risk factors studied, there were 16 significant positive and one significant negative associations (see Table 26), none of which could be explained by adjustment for social class.

(d) More recently conducted analyses [95], based on the Health Survey for England 1993 [84], a very large, representative study in which cotinine in serum had been determined, allowed the same general conclusions to be reached. These analyses, which used a somewhat different list of risk factors from those used for the UK Health and Lifestyle Survey, due to differences in the questions asked in the two

surveys, found 12 significant positive and one significant negative association (see Table 27). Again adjustment for social class did not explain these relationships.

(e) The epidemiological studies of ETS and lung cancer paid only very little attention to potential confounding variables. Thus, not only were known risk factors adjusted for in very few studies, e.g. occupation in only six and diet in only three, but many of the studies also failed to exclude unmarried women from unexposed groups in analyses using smoking by the husband as the index of ETS exposure (and also failed to exclude unemployed women from analyses using smoking in the workplace as the index). It is also notable that about a quarter of the studies did not even adjust for age, and that the relative risk for husband smoking varied highly significantly ($p<0.001$) according to how the study took account of age. In the 32 studies which either adjusted for age in analysis and/or matched the never smoking cases and controls for age, the relative risk was 1.10 (95% CI 1.02-1.18). In contrast, in the 12 studies which did not, the relative risk was much higher - 1.53 (95% CI 1.30-1.81). Many of these 12 studies matched overall cases and controls on age, but made no attempt to ensure the never smoking cases and controls drawn from them were still of similar age. Appendix J illustrates how false conclusions can readily arise due to the failure of age matching.

The meta-analyses of data for husband's smoking adjusted, where possible, for covariates, gave a relative risk, 1.16 (95% CI 1.09-1.25), which was 0.03 less than that using unadjusted data throughout, 1.19 (95% CI 1.11-1.28). It is very difficult to assess accurately how much the relative risk would have been further reduced had full adjustment for covariates been made in all studies. It certainly does not seem unreasonable to assume that the additional reduction could have been substantial.

13.6 Recall bias

Of the 44 epidemiological studies of lung cancer and husband's smoking considered in Table 2, only five are of prospective design. Two of these [19, 24] involved less than 10 lung cancer cases, so adding little to the debate, and two further

studies [1, 37], though based on over 150 deaths, did not demonstrate a statistically significant relationship. Only one prospective study, that of Hirayama [6], has reported a statistically significant relationship. That study, though based on 200 lung cancer deaths in women, is open to considerable criticism, as described in Appendix F. Although the combined evidence from the five prospective studies shows a marginally significant ($p<0.05$) relationship (see Table 3), it is clear that it does not provide convincing evidence of an association.

The major contributor to the highly significant ($p<0.001$) overall relationship between lung cancer and husband's smoking shown in Table 25 is the evidence from the 39 case-control studies. One particular problem with case-control studies is that the evidence relating to the cases is collected after diagnosis of lung cancer and the validity of the data collected may be affected by presence of, or knowledge of, the disease [76]. Lung cancer cases (or surrogate respondents for them) may be more ready to recall ETS exposure, in an attempt to rationalize their disease, than either healthy controls or controls with diseases not widely reported to be associated with ETS exposure. There is little direct evidence of such recall bias in the literature on ETS and lung cancer. However, it remains a possible source of bias. Theoretically it is perhaps less likely to affect analyses based on simple exposure indices such as smoking by the husband than it is to affect analyses based on estimation of extent of exposure quantitatively or semi-quantitatively. The evidence on dose-response relationships is particularly likely to be subject to recall bias, especially since the various indices used were never determined objectively, always relying on the subjective assessment of the respondent.

13.7 Bias due to lack of comparability of cases and controls

A standard principle of good experimental design is to compare "like with like." It follows that, in case-control studies, care should be taken to avoid systematic differences in which the data are collected for cases and controls. It is clear that this principle was not adhered to in a number of studies where, for example, the cases might have been alive or dead, and the controls were not matched on vital status, the proportion of proxy respondents was substantially higher for cases than for controls, the cases and controls came from different hospitals, or the cases and controls were interviewed in

different places. In an attempt to gain some idea of the effect such systematic differences might have had, Lee [69] defined studies as being of poor quality if they had any of the four weaknesses referred above or any of three other weaknesses - very small study size - less than 10 lung cancer cases; all respondents next-of-kin; or no details provided on controls. Based on these criteria, which admittedly constitute only a few of the many ways in which study weaknesses could be quantified, it can be shown that the 21 "inferior" studies had a combined covariate-adjusted relative risk (1.24, 95% CI 1.12-1.38) for husband's smoking which was almost significantly ($0.05<p<0.1$) higher than that for the 23 "superior" studies (1.10, 95% CI 1.00-1.21). This gives some support for concluding that weakness in study design may have contributed to the elevated risk of lung cancer associated with husband's smoking.

13.8 Diagnostic bias

A recent review of the published evidence on accuracy of lung cancer diagnosis concluded that a not insubstantial proportion of clinical and death certificate diagnoses are not confirmed at autopsy [74]. Especially because histological confirmation was not insisted upon in over half the 44 studies providing evidence on lung cancer and spousal smoking, it is likely that a proportion of the cases considered to be primary lung cancer were in fact misdiagnosed. The extent to which such misdiagnosis might have biased the overall relative risk estimate is difficult to assess. Random misclassification with diseases unassociated with ETS would lead to underestimation of any true relationship, but it is not totally clear whether misclassification is random (misdiagnosis might be correlated with ETS exposure itself, or with factors associated with ETS), or whether ETS is unassociated with all diseases that might be confused with lung cancer (e.g. other cancers or other lung diseases). The fact that relative risks were higher for studies where 100% histological diagnosis was insisted upon (1.28, 95% CI 1.15-1.43) than for the other studies where it was not (1.09, 95% CI 1.00-1.19) suggests that, if there is a true relationship between ETS and lung cancer, it may have been underestimated by diagnostic inaccuracy.

13.9 Publication bias

It is well documented that, in many situations scientists tend not to submit, or journals not to publish, results from studies which find no effect. The question arises

whether such publication bias could have affected the representativeness of the published evidence on ETS and lung cancer. Some indication of publication bias can be seen from the fact that meta-analysis relative risks for husband's smoking show significant ($p<0.05$) heterogeneity by study size, with estimates lower for studies with more than 100 lung cancer cases than for studies with fewer than 100 cases. This observation is consistent with failure to publish results from small studies that reported a lack of association, or even a negative association, between lung cancer and smoking by the husband.

It can, of course, be argued that failure to publish a few small studies would have little effect on the overall relative risk estimate and that it is failure to publish large studies that is more important. In view of the interest in ETS as a possible risk factor for lung cancer, and the effort involved in conducting a large study, it might be thought that large studies would be published. That this is not necessarily so is seen in the case of the huge second American Cancer Society prospective study, for which results on active smoking and lung cancer were published as long ago as 1981 [90]. To this date the results for ETS and lung cancer, which show no significant relationship whatsoever for any index and for either sex, have never been published in a journal. The author of this review only became aware quite recently that the findings had been presented in a doctoral dissertation in 1994 [37], relative risks from this study having not previously been included in any published meta-analysis. It is interesting to speculate how quickly the results would have been published had a significant association been found!

13.10 Biases particularly relevant to dose-response data

In interpreting the association between lung cancer and smoking by the husband, some [53,96] have placed considerable emphasis on the quite consistent evidence of a dose-response relationship. However, due to a number of well-documented methodological problems, it would actually be expected that the data from the ETS and lung cancer epidemiological studies, or at least those based upon spousal smoking, would exhibit evidence of a dose-response relationship even in the absence of causality. These methodological problems include:

(a) **Confounding**. Exposure to many lung cancer risk factors other than chemicals present in smoke is increased in smokers in relation to the amount they smoke,

and is also increased in nonsmokers in relation to living with a smoker, partly because people living together share many habits in common [70]. On this basis, it is only to be expected that exposure to these risk factors is also likely to be increased in nonsmokers in the household in relation to the amount smoked by the husband. Similarly it also follows that the longer a nonsmoker has been exposed to the husband's smoking, the longer the nonsmoker will have to be exposed to these non-tobacco lung cancer risk factors. Thus a dose-response relationship in lung cancer risk in nonsmokers would be expected, both in relation to the amount and the duration of the husband's smoking, as a result of confounding by these other risk factors [49,60].

(b) **Misclassification of smoking habits**. Concordance of smoking habits between spouse increases with amount smoked [77]. For a given misclassification level, therefore, the magnitude of the misclassification bias will increase with amount smoked, also creating an apparent dose-response relationship.

(c) **Publication bias**. A combined relative risk estimate for husband's smoking for the 28 studies providing dose-response data is 1.24 (95% CI 1.14-1.35) while that for the other 16 studies is 1.02 (95% CI 0.90-1.15). These estimates are significantly different ($p<0.05$), indicating that studies presenting dose-response data are unrepresentative of all studies reported. This is consistent with investigators being more likely to look for evidence of a dose-response relationship if their data happen in the first place to suggest that risk is greater if the husband smokes. Both trend tests including the unexposed group and tests comparing risk in the highest and unexposed groups are highly correlated with the simpler test of comparing risk when the husband smokes with risk when he does not smoke. Thus, it is hardly surprising that these tests tend to be positive, being based on a biased subset of studies which show an abnormally high, and significant, increased risk when the husband smokes.

(d) **Recall bias**. In case-control studies, lung cancer cases (or their proxy respondents) may overstate spousal cigarette consumption, relative to controls, in an attempt to rationalize their disease state. This would have the effect of creating or exaggerating differences in cigarette consumption between the husbands of cases and controls. Note that recall bias is more likely to be relevant

to the extent (or duration) of smoking by the spouse than to whether or not the spouse smoked, so being of particular importance for dose-response analyses. Recently it has been clearly shown [97] that it would only take quite modest recall bias to explain the significant association reported in the large study by Fontham [36] between lung cancer and pack years of ETS exposure from the husband. That paper referred to a number of studies [98-103] demonstrating substantial problems with the reliability of self reports of ETS exposure.

(e) **Trend tests**. Although the practice of interpreting statistical tests for trend as evidence for a dose-response relationship is widespread, it has been questioned [76,104]. Breslow and Day [76] caution that there is a greater possibility that bias and confounding could produce a dose-response function which rises initially and then becomes flat. They suggest excluding the baseline non-exposed category when testing specifically for a dose-response effect. In the case of the spousal studies of ETS and lung cancer, only two of 10 significant positive trends obtained from a test including the unexposed group remained significant when the unexposed group was excluded, and in both these cases the significance resulted in part from relative risks less than 1.0 in the lowest exposed category. Indeed, none of the 40 dose-response data sets analyzed showed a monotonically increased pattern for which the trend including and excluding the unexposed group was statistically significant.

Considered as a whole, the above points make it clear that the evidence relating to the existence of a dose-response relationship is much weaker than has been suggested.

13.11 Evidence of inconsistency

As seen in Table 25, the association of ETS with lung cancer is inconsistent in that it is evident for spousal smoking, but not for workplace, childhood or social ETS exposure. As shown in Section 4, there are also a number of indications of inconsistency within the data for smoking by the husband. Thus, there is inconsistency:

(i) between continents, with relative risks higher in Europe than in the US and Asia;

(ii) between countries within Asia, with evidence of an association in Japan and Hong Kong, but not China;

(iii) over time, with the association clearly stronger in studies published in the 1980s than in those published since then;

(iv) by study size, with relative risks higher for smaller than for larger studies;

(v) by study quality, with relative risks higher for studies classified as of poorer quality;

(vi) by study type, with relative risks higher in case-control studies using "diseased" rather than "healthy" controls;

(vii) by histological type, with some studies suggesting a stronger relationship with squamous carcinoma and others with adenocarcinoma;

(viii) by histological confirmation, with relative risks higher for studies that required this for all cases;

(ix) by whether some confounding variables were taken into account, with relative risks higher for studies where none were; and

(x) by whether dose-response relationships were studied, with relative risks higher for studies where they were.

While these associations generally are statistically significant, considered individually, they do not all represent independent relationships (see Appendix I), inasmuch as some of these study characteristics are correlated. Taken together, however, they cast further doubt on the view that the association with husband's smoking indicates a causal relationship. This is emphasized by realizing that the magnitude of the differences in relative risk associated with some study characteristics is greater than the magnitude of the elevation in relative risk associated with smoking by the husband.

13.12 Relevance of supporting evidence

Some pieces of evidence bear on the possibility of a true relationship between ETS exposure and lung cancer.

Animal studies

No inhalation studies of ETS beyond 90 days have been conducted in animals. The 90 day studies [105,106] did not suggest any carcinogenic effect of ETS exposure. Claims that ETS has been shown to be carcinogenic in animals [55] have been clearly demonstrated [107] to be inappropriately based upon studies of animals exposed to mainstream tobacco smoke or to exaggerated concentrations of fresh sidestream smoke.

It has been reported [108] that dogs with lung cancer were more likely to have a smoker in the home than were dogs with other cancers. The relative risk estimate of 1.6 was not, however, statistically significant (95% CI 0.7-3.7).

Pathology study

An autopsy-based study conducted in Athens [109] found a significantly higher mean score of "epithelial, possibly precancerous lesions" (EPPL) in nonsmoking women married to smokers compared with women married to nonsmokers, and concluded that "these results provide support to the body of evidence linking passive smoking to lung cancer." However, these results are uninterpretable in that, in smokers, EPPL was negatively related to amount smoked, with no difference in mean value between heavy smokers (>41 cigs/day) and nonsmokers. Although the methodology used in the study was purportedly inspired by an earlier study [110], that study showed, in complete contrast, a strong dose-related response in smokers with a very low incidence of pathological change in nonsmokers.

DNA adduct data

An increased level of 4-aminobiphenyl-haemoglobin adducts has been reported in relation to both smoking and level of ETS exposure [111]. However, the authors commented that the increase is not dramatic, and the public health significance is unclear. Protein and DNA adducts have been used as biomarkers of exposure to environmental

chemicals for some years, but there are still only a few examples of definitive identification of DNA adducts and much to be learned about their origin. More important still is the question of the relative biological significance of adducts that are endogenous and those that are of environmental origin. Certainly observation of an increased level of adducts in relation to ETS exposure in one study does not allow the inference that ETS is necessarily carcinogenic to humans [112].

13.13 Overall conclusion

Although the ETS inhaled by nonsmokers and the mainstream smoke inhaled by smokers contain many chemicals in common, differences in chemical and physical composition of the two types of smoke mean that ETS cannot be considered as a dilute form of mainstream smoke [113,114]. Even if it could, the low concentrations of the chemicals in ETS, which are typically very many times lower than permissible exposure limits approved by regulators [115], would not imply that any carcinogenic effect of ETS can be assumed. This is consistent with the views of the majority of toxicologists, who no longer believe in the zero threshold for carcinogenesis [116]. If there is an effect of ETS on the risk of lung cancer, it needs to be demonstrated by epidemiological or experimental evidence.

It is clear, however, that the evidence available does not convincingly demonstrate that ETS exposure increases the risk of lung cancer. The experimental evidence is completely lacking, as noted in Section 13.12. The epidemiological evidence, which has been examined in detail in this review, is also unconvincing. There is no evidence of a relationship between lung cancer and ETS exposure in childhood, in the workplace or social situations. While there is evidence of an association between spousal smoking and lung cancer risk, this is affected by a number of sources of bias. Adjustment for plausible levels of bias due to smoking habit misclassification has been shown to reduce very substantially the magnitude of the association reported with husband's smoking. Uncontrolled confounding, publication bias and recall bias may also contribute to the observed association. Unexplained variations in relative risk by various study characteristics, often as large as, if not greater than, the magnitude of the increase associated with smoking by the husband, further undermine the validity of drawing a

causal inference from the data.

The overall conclusion to be drawn is that the data, taken as a whole, are consistent with ETS exposure having no effect on the incidence of lung cancer.

In the final chapter of this review, this conclusion is contrasted with those of four other recent published reviews [53,55,56,58]. It is demonstrated that differences in conclusions reached result from a series of evident weaknesses in these reviews.

14. Weaknesses of earlier reviews by other authors

14.1 Introduction

In this section we comment briefly on four recent published reviews of the evidence on ETS and lung cancer, by the US Environmental Protection Agency (EPA) [53], by the US Occupational Safety and Health Administration (OSHA) [55], by a group of epidemiologists associated with the International Agency for Research on Cancer (IARC) [56], and by two epidemiologists at the Wolfson Institute of Preventive Medicine, St Bartholomew's Hospital Medical College (BARTS) [58]. Detailed examination of these reports reveals a number of weaknesses. Some of these are summarized in the sections that follow.

14.2 Failure to recognise the possibility of a threshold dose

A remarkable statement in the BARTS review is that "the **observation** that carcinogens have no threshold indicates that inhaled tobacco smoke **must** increase the risk of lung cancer". In fact, it is in principle impossible to observe either presence or absence of a threshold; at best one can consider the data consistent with a mechanism which would or would not imply existence of a threshold. As the mechanism by which tobacco-associated cancer arises is unknown, it is little more than speculation to estimate risks by extrapolation using a linear no-threshold model. There is a wide body of opinion supportive of the view that a threshold is likely to exist for cancer arising by a non-genotoxic mechanism. Even where a genotoxic mechanism pertains, absence of a threshold cannot be inferred with any confidence [116]. As Doll states [117] "we are constantly faced with the problem of deciding whether linearity continues to hold at very low levels or whether there is some biological mechanism - for example, an error-free repair mechanism or a stress reaction - that modifies or even eliminates the effect."

IARC only consider it **"likely"** that ETS exposure will cause lung cancer, based on extrapolation from active smoking data.

EPA concluded that ETS should be categorized a Group A (human) carcinogen because they consider mainstream smoke to cause lung cancer, mainstream and sidestream smoke to have "extensive chemical and toxicological similarities", ETS to be

composed of sidestream and exhaled mainstream smoke, and because ETS is known to be inhaled and absorbed into the body. Their categorization processes do not seem to allow for the possibility of a threshold.

OSHA did not attempt to argue that ETS exposure must cause lung cancer based on a no-threshold argument.

14.3 Extrapolation from risk in smokers

BARTS state that "In non-smokers married to smokers, the exposure to tobacco smoke is about 1% that of actively smoking 20 cigarettes per day (based on concentrations of cotinine, the principal metabolite of nicotine)". Using the fact that "the last 20 years follow-up in the British Doctors Study demonstrated an excess risk of about 20-fold associated with actively smoking 20 cigarettes per day" they concluded that "the expected excess risk in non-smokers passively exposed, from linear dosimetry, would be 20%, and the relative risk 1.2."

Leaving aside the question of the validity of extrapolation using a linear no-threshold model, there are a number of criticisms and comments that can be made of the way that the extrapolation has been conducted:

1. Particulate matter, not nicotine, has long been considered to be the agent involved in smoking-related lung cancer [52]. Why do Law and Hackshaw use a marker based on nicotine? Relative retention for passive and active smokers is much lower based on particulate matter, perhaps of the order of 0.05% [54], than the 1% Law and Hackshaw cite based on cotinine.

2. While nicotine is predominantly in the particulate phase in mainstream smoke, it is predominantly in the vapour phase in ETS. Cotinine is therefore an index of exposure to different ranges of chemicals when used for smoking and for ETS exposure. As Bayard et al of the EPA, state [96], cotinine might be used "to estimate relative exposures among different passive smokers to the entire ETS mixture" but "should not be used to extrapolate from active to passive smoking

exposures."

3. The epidemiological evidence on marriage to a smoker and lung cancer is typically based on studies using the exposure index "spouse ever smoked" not "spouse currently smokes 20 cigs/day" as Law and Hackshaw's extrapolation implicitly assumes. On this basis the comparison should be, not with the relative risk of 20 for current smoking of 20 cigs/day, but with the relative risk for ever having smoked, which is much lower, perhaps about 8.

4. Furthermore, the epidemiological evidence on marriage to a smoker and lung cancer is predominantly based on studies in women. Active smoking relative risks are lower for women than for men.

5. It has been reported that the relationship between the risk of lung cancer and number of cigarettes smoked per day is not linear, but has a quadratic component [91]. Based on this relationship, it can be calculated that exposure to 1% of 20 cigarettes per day would not reduce the excess risk by a factor of 100 but by a factor of 262.

Using a relative exposure of 0.05% not 1%, and relative risks of 8 or less, not 20, would reduce the risk of ETS-related lung cancer predicted by a linear no-threshold model by over 50 fold. Further assuming a quadratic component in the dose-response relationship would reduce it more than 100 fold, predicting a relative risk less than 1.002.

14.4 Inappropriate selection of data for overview

The list of studies considered by OSHA and IARC is open to criticism. OSHA's list of studies considered excludes, for no apparent reason, four studies published some years before their report [1,9,23,29], excludes four more recent studies which they could have included [30,31,34,35] and includes a few studies that have been excluded in my review (for reasons described in Appendix A).

While IARC included all the relevant early studies they excluded a number of

studies [9,19,20,21,30] which are considered in the EPA report. The omissions were stated to be because of "major methodological limitations" or "very limited information", but no attempt was made to define criteria for exclusion or to discuss what these limitations were.

More seriously, IARC gave a misleading impression of data published in the 1987-1993 period by failing to attempt to present results systematically by one exposure index. Of the 15 studies considered, there were only seven for which spousal smoking data were appropriately cited. In the case of the other eight studies, the data cited were not for the appropriate index of exposure. As can be seen from Table 28 the inappropriately cited data **always** had substantially higher relative risks than the data that should have been cited (and which EPA, BARTS and this review have used). The effect of this was to distort the evidence dramatically.

14.5 Inappropriate use of 90% confidence intervals

Whereas earlier major reviews of the evidence on ETS and lung [48,49] followed generally accepted practice and used 95% confidence intervals, EPA used 90% confidence intervals without justification. It is only by using 90% confidence intervals and inadequate correction for smoking habit misclassification that the meta-analysis relative risk for the US becomes "statistically significant". Had this relative risk not been statistically significant, risk assessment could not have been carried out according to their rules.

14.6 Failure properly to consider data for indices of exposure other than spousal smoking

Despite the extensive nature of their report, the EPA restrict attention to spousal smoking, because studies of exposure from other sources "are fewer and represent fewer cases", while OSHA make no attempt to review evidence on workplace ETS exposure despite the fact that their whole purpose was to propose restrictions on smoking in the workplace. BARTS do not even mention the existence of evidence other than that relating to spousal smoking. Though IARC do note that data are available for various sources of ETS exposure, they make no attempt to review these data systematically, and thus do not make it clear the association with lung cancer is restricted to spousal

smoking, nor the effect this has on the interpretation of the overall evidence.

OSHA show quite remarkable bias by selecting results from one study [36] that happened to show an association of lung cancer with workplace ETS exposure, ignoring totally results from a large number of studies that did not (see Table 16).

14.7 Failure to recognize sources of heterogeneity in the data

BARTS state that "the estimate from each individual study is consistent with the overall estimate" implying lack of statistically significant heterogeneity. In fact the overall evidence for smoking by the spouse shows quite highly significant heterogeneity. Even had it not done so, it would have been appropriate to investigate whether relative risk estimates differed significantly according to specific study characteristics, but BARTS did not attempt this. Only EPA investigate sources of heterogeneity, and then they restrict attention only to regional variation, not looking at any of the sources considered in Section 4. IARC give the impression that the overall strength of the association between lung cancer and husband's smoking has changed little since that reported in reviews conducted 10 years or so ago. In fact, this false impression arises because they do not carry out any formal meta-analysis of the data and also because the data they cite for the later studies are often inappropriate (see Section 14.4)

14.8 Failure to consider histological type of lung cancer

No attempt is made by EPA, BARTS or IARC to compare and contrast results for different histological types of lung cancer. OSHA state that "similar tumor cell types are induced by ETS exposure as are induced by active smoking" without noting the very much stronger association of active smoking with squamous/small cell lung cancer than with adenocarcinoma/large-cell lung cancer, or the inconsistent nature of the association with ETS exposure.

14.9 Failure to adjust properly for bias due to misclassification of active smoking status

Of the four reviews considered, only EPA formally attempt to adjust for bias due to misclassification of active smoking status. However, as is made clear in recently published papers [63,64], their method of adjustment is mathematically incorrect, and they assume levels of misclassification that are inappropriately low, particularly for Asia, where recent evidence from two studies [79,80] indicates very much higher levels of exposure than seen in Western populations. IARC rely on the results of the EPA analyses, while for their conclusions BARTS falsely claim, based only on a paper written ten years ago, long before the relevant evidence on an extent of misclassification and proper methods for adjustment for bias became available, that the effect of bias due to misclassification of active smoking status is approximately cancelled out by the effect of bias arising because non-smokers living with non-smokers do not have zero ETS exposure. If, in fact, adjustment of bias due to misclassification of active smoking habits removed the whole association with husband's smoking, as it may well do for the data for the US, Asia and Western Europe (See Section 4.11), then the two biases cannot possibly cancel out, since the second bias only operates at all if a true association can be shown to exist after adjustment for smoking habit misclassification

OSHA noted that the Fontham study [36] "controlled for misclassification to a large degree", not realizing that the procedures adopted in that study may have exacerbated bias due to misclassification, not reduced it (see Section 13.4). They also considered bias due to misclassification of smoking to be only of minor importance, when a proper analysis shows it to have a major effect.

14.10 Confounding by other risk factors as a source of systematic bias

The section on potential confounders is one of the weakest parts of the EPA report. In the first place, the apparent objectives are wrong with EPA requiring a **single** confounding variable to explain **fully** the significant association of ETS exposure with lung cancer in Greece, Hong Kong, Japan and the United States. Why should it not be part of the story only, with other confounders and other sources of bias also being relevant? Secondly, in attempting to determine whether a specific risk factor is a cause of lung cancer they totally unreasonably limit attention to the ETS/lung cancer evidence,

ignoring the massive literature available from lung cancer studies which investigated the risk factor of interest, but not ETS.

BARTS note that "There is potential for confounding because the dietary intake of antioxidant vitamins (carotenes/vitamin A and vitamin C) is lower in non-smokers married to smokers than in non-smokers married to non-smokers, and low levels of these vitamins may increase the risk of lung cancer independently of smoking." However they point out that "the risk estimate for environmental tobacco smoke exposure was not materially altered" in the "three epidemiological studies of passive smoking and lung cancer" which "controlled for the effect of diet."

This discussion is inadequate. They do not make it clear that there are a large number of risk factors for lung cancer, that there is also growing evidence that ETS exposure is associated with increased exposure to a variety of lifestyle factors linked to adverse health [70; Tables 26 and 27], and that attention to confounding in many of the studies of ETS and lung cancer has been non-existent or very limited (see Appendix C).

The discussion on potential confounders by IARC is rather better but the general point is not made that ETS exposure is systematically associated with increased exposure to a whole range of lifestyle risk factors.

OSHA do not even mention confounding at all!

14.11 Publication bias

Publication bias was simply not addressed by EPA or BARTS, and reasons for believing that it exists were not considered by OSHA. IARC refer to some early published works on the subject, but do not actually test for its existence using the data they present.

14.12 Recall bias

OSHA argue that, because the results from case-control studies and prospective studies are similar, recall bias is not important. Actually this is not strong evidence, because of the limited nature of the data from the prospective studies. IARC merely refer to the finding from the Fontham study [36] that relative risks were similar whether cancer or general population control groups were used. EPA noted recall bias may exist but did not discuss its likely importance. BARTS did not mention recall bias.

14.13 Failure to test for effects of study weaknesses

The EPA conducted an exercise classifying studies as weak or strong according to various criteria. Surprisingly, however, they did not compare relative risk estimates of the groups of studies so classified.

OSHA did not even suggest that any of the specific epidemiological studies it considered might have fundamental weaknesses that render interpretation difficult or impossible. Nor did BARTS or IARC.

14.14 Failure to point out the possibility of increased bias in the highest exposure group

EPA make great stress in their report of the fact that all the 17 individual studies that they considered which had data by exposure level showed a relative risk greater than 1 for the highest exposure category. They did not point out the considerable problems due to publication/selection bias of the results, with studies that found an overall association between spouse smoking and lung cancer risk tending to present dose-response data, while many studies that did not find an association did not present such data. Nor do they note that misclassification bias, confounding, and recall bias are all likely to produce an artefactual dose-response relationship.

IARC noted the existence of a dose-response relationship, more so with amount smoked than with years smoked, but did not even consider any of the forms of bias that might have produced this.

Remarkably neither OSHA nor BARTS even refer to dose-response relationships

at all!

14.15 Inappropriate method of extrapolation to estimate total lung cancer deaths associated with ETS exposure

Having estimated the misclassification-adjusted relative risk of lung cancer associated with husband's smoking, the EPA then attempted to estimate the total number of lung cancer deaths in the USA associated with ETS exposure. This further estimation made three assumptions:

(i) that the association between lung cancer and overall ETS exposure could be computed from the estimated association between lung cancer and smoking by the husband, based on data on relative cotinine levels in nonsmokers married to a nonsmoker;

(ii) that the estimated association between lung cancer and husband's smoking could be assumed to apply also to the association between lung cancer and wife's smoking;

(iii) that the association between lung cancer and husband's smoking estimated for nonsmokers also applied to ex-smokers.

Of these assumptions the first ignores the available data that exists on the association between lung cancer and other sources of ETS exposure than the husband, the second ignores the available data that exists in relation to wife's smoking, while the third is unsupported, and not particularly plausible. Furthermore, the estimate of relative cotinine level used, of 1.75, is far too low, being much less than reported in a recent huge representative study of the US using state-of-the-art analytical methodology [118].

OSHA attempted to carry out quantitative risk extrapolation based solely on data from the Fontham study [36] without noting any of its problems (see Appendix F). Its atypical findings for workplace exposure are particularly relevant.

IARC and BARTS did not attempt such extrapolation procedures.

15. Acknowledgements

I thank Mrs B A Forey for considerable help in assembling the database and for programming, and Dr F J C Roe, Dr A Springall and Dr J S Fry for helpful comments. I also thank Mrs P Wassell and Mrs F Lennard for typing the numerous drafts and Mrs K J Young for detailed checking of this report. I am grateful to various tobacco companies for providing financial support.

I alone bear responsibility for the views expressed.

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TABLE 1

Studies providing information on risk of lung cancer in relation to ETS exposure in lifelong nonsmokers

Study					Number of lung cancers in lifelong nonsmokers	
Ref	Author	Year	Location	Type	Females	Males
1	Garfinkel 1	1981	USA	P	153	
2	Chan	1982	Hong Kong	CC	84	
3	Correa	1983	USA/Louisiana	CC	25	10
4	Trichopoulos	1983	Greece/Athens	CC	77	
5	Buffler	1984	USA/Texas	CC	41	11
6	Hirayama	1984	Japan	P	200	64
7	Kabat 1	1984	USA/New York	CC	53	25
8	Garfinkel 2	1985	USA/New Jersey, Ohio	CC	134	
9	Lam W	1985	Hong Kong	CC	75	
10	Wu	1985	USA/California	CC	31	
11	Akiba	1986	Japan/Hiroshima, Nagasaki	CC	94	19
12	Lee	1986	England	CC	32	15
13	Brownson 1	1987	USA/Colorado	CC	19	
14	Gao	1987	China/Shanghai	CC	246	
15	Humble	1987	USA/New Mexico	CC	20	8
16	Koo	1987	Hong Kong	CC	88	
17	Lam T	1987	Hong Kong	CC	202	
18	Pershagen	1987	Sweden	CC	83	
19	Butler	1988	USA/California	P	8	
20	Geng	1988	China/Tianjin	CC	54	
21	Inoue	1988	Japan/Kanagawa	CC	28	
22	Shimizu	1988	Japan/Nagoya	CC	90	
23	Choi	1989	Korea	CC	75	13
24	Hole	1989	Scotland/Paisley, Renfrew	P	6	3
25	Svensson	1989	Sweden/Stockholm	CC	38	
26	Janerich	1990	USA/New York	CC	146	45
27	Kalandidi	1990	Greece/Athens	CC	91	
28	Sobue	1990	Japan/Osaka	CC	144	
29	Wu-Williams	1990	China/Shenyang, Harbin	CC	417	
30	Liu Z	1991	China/Xuanwei	CC	54	
31	Joeckel	1991	Germany/Bremen, Frankfurt	CC	23	10
32	Brownson 2	1992	USA/Missouri	CC	432	
33	Stockwell	1992	USA/Florida	CC	210	
34	Liu Q	1993	China/Guangzhou	CC	38	
35	Du	1993	China/Guangzhou	CC	75	
36	Fontham	1994	USA/Atlanta, Houston, LA, New Orleans, San Francisco Bay	CC	653	
37	Cardenas	1994	USA	P	246	116
38	Layard	1994	USA	CC	39	21
39	Zaridze	1994	Russia/Moscow	CC	162	
40	Kabat 2	1995	USA/New York, Chicago, Detroit, Philadelphia	CC	69	41
41	de Waard	1995	Holland/Utrecht	CC	23	
42	Shen	1996	China/Nanjing	CC	70	
43	Sun	1996	China/Harbin	CC	230	
44	Wang S-Y	1996	China/Guangzhou	CC	82	
45	Wang T-J	1996	China/Shenyang	CC	135	
46	Schwartz	1996	USA/Detroit	CC	185	72
	Total				5480	473

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.

The study year is the year of that publication.

The two study types are CC=case control and P=prospective.

Numbers of lung cancers in lifelong nonsmokers are totals in the study; for analyses relating to specific types of exposure numbers may be less than this.

Studies 41 and 42 do not provide data on spousal smoking.

TABLE 2

Relative risk of lung cancer among lifelong nonsmoking women in relation to smoking by the husband

Study		Number of lung cancer cases	Unadjusted data		Covariate adjusted data	
Ref	Author		Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
1	Garfinkel 1	153	1.17(0.85-1.61)	1.18(0.90-1.54)		
2	Chan	84	0.75(0.43-1.30)			
3	Correa	22	2.07(0.81-5.25)			
4	Trichopoulos	77	2.08(1.20-3.59)+			
5	Buffler	41	0.80(0.34-1.90)			
6	Hirayama	200	1.38(0.97-1.98)	1.45(1.02-2.08)		+
7	Kabat 1	24	0.79(0.25-2.45)			
8	Garfinkel 2	134	1.23(0.81-1.87)			
9	Lam W	60	2.01(1.09-3.72)+			
10	Wu	28	1.41(0.54-3.67)	1.20(0.50-3.30)		
11	Akiba	94	1.52(0.87-2.63)	1.50(0.90-2.80)		
12	Lee	32	1.03(0.41-2.55)	1.00(0.37-2.71)		
13	Brownson 1	19	1.52(0.39-5.96)	1.68(0.39-6.90)		
14	Gao	246	1.19(0.82-1.73)			
15	Humble	20	2.34(0.81-6.75)	2.20(0.80-6.60)		
16	Koo	86	1.55(0.90-2.67)	1.64(0.87-3.09)		
17	Lam T	199	1.65(1.16-2.35)+			
18	Pershagen	70	1.03(0.61-1.74)	1.20(0.70-2.10)		
19	Butler	8	2.44(0.58-10.22)		2.02(0.48-8.56)	
20	Geng	54	2.16(1.08-4.29)+			
21	Inoue	22	2.55(0.74-8.78)	2.25(0.80-8.80)		
22	Shimizu	90	1.08(0.64-1.82)			
23	Choi	75	1.63(0.92-2.87)			
24	Hole	6	1.89(0.22-16.12)			
25	Svensson	34	1.26(0.57-2.81)			
26	Janerich	144	0.75(0.47-1.20)			
27	Kalandidi	90	1.62(0.90-2.91)	2.11(1.09-4.08)		+
28	Sobue	144	1.06(0.74-1.52)	1.13(0.78-1.63)		
29	Wu-Williams	417	0.79(0.62-1.02)	0.70(0.60-0.90)		-
30	Liu Z	54	0.74(0.32-1.69)	0.77(0.30-1.96)		
31	Joeckel	23	2.27(0.75-6.82)			
32	Brownson 2	431	0.97(0.78-1.21)	1.00(0.80-1.20)		
33	Stockwell	62	1.60(0.80-3.19)	1.60(0.80-3.00)		
34	Liu Q	38	1.66(0.73-3.78)			
35	Du	75	1.09(0.64-1.85)			
36	Fontham	651	1.26(1.04-1.54)+	1.29(1.04-1.60)		+
37	Cardenas	164	1.10(0.79-1.53)	1.10(0.80-1.60)		
38	Layard	39	0.63(0.33-1.21)	0.58(0.30-1.13)		
39	Zaridze	162	1.66(1.12-2.45)+	1.66(1.12-2.46)		+
40	Kabat 2	67	1.10(0.62-1.96)	1.08(0.60-1.94)		
43	Sun	230			1.16(0.80-1.69)	
44	Wang S-Y	82	2.53(1.26-5.10)+			
45	Wang T-J	135	1.11(0.67-1.84)			
46	Schwartz	185	1.18(0.77-1.81)	1.10(0.72-1.68)		

Footnotes

In eight studies (2, 5, 13, 24, 25, 30, 44, 46) the index of exposure is not actually based on husband's smoking, but on the nearest equivalent index (see Table 14).

The study author is the name of the first author in the publication from which the data were extracted; see references.

For two studies (1,37) the data in the unadjusted column are adjusted for age, and in the adjusted column are adjusted for age and other risk factors.

See Appendix B for details of how the data were extracted from the source publication.

See Appendix C for the covariates considered in adjusted analyses.

Significant ($p<0.05$) positive relative risks are indicated by + with significant negative risks indicated by -.

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TABLE 3

Meta-analyses of data for husband's smoking

	Number of studies	Unadjusted data: Relative risk (95% CI)	Signi-ficance	Heterogeneity: Within	Heterogeneity: Between	Data adjusted for covariates: Relative Risk (95% CI)	Signi-ficance	Heterogeneity: Within	Heterogeneity: Between
All studies	44	1.19(1.11-1.28)	+++	*		1.16(1.09-1.25)	+++	***	
	44 R	1.23(1.12-1.36)	+++	*		R 1.24(1.12-1.39)	+++	***	
Continent									
USA	17	1.12(1.01-1.24)	+	NS	NS	1.12(1.01-1.24)	+	NS	*
Europe	8	1.52(1.22-1.90)	+++	NS		1.62(1.29-2.04)	+++	NS	
Asia	19	1.20(1.08-1.34)	+++	*		1.13(1.02-1.26)	+	***	
	19 R	1.27(1.09-1.50)	++	*		R 1.27(1.08-1.53)	++	***	
Country within Asia									
Japan	5	1.26(1.02-1.55)	+	NS	NS	1.30(1.05-1.60)	+	NS	*
Hong Kong	4	1.44(1.13-1.84)	++	NS		1.45(1.13-1.86)	++	NS	
China/Korea	10	1.10(0.95-1.27)	NS	*		1.00(0.87-1.14)	NS	***	
Publication date (1)									
1981-89	25	1.36(1.21-1.52)	+++	NS	**	1.36(1.22-1.52)	+++	NS	***
1990-96	19	1.10(1.01-1.20)	+	*		1.06(0.97-1.16)	NS	***	
Publication date (2)									
1981-86	12	1.29(1.11-1.51)	++	NS	***	1.29(1.11-1.50)	+++	NS	***
1987-89	13	1.43(1.21-1.70)	+++	NS		1.46(1.23-1.73)	+++	NS	
1990-92	8	0.96(0.84-1.09)	NS	NS		0.92(0.81-1.03)	NS	**	
1993-96	11	1.23(1.09-1.39)	+++	NS		1.23(1.09-1.39)	++	NS	
Considered by ISCSH 3rd and 4th reports									
Yes	12	1.31(1.14-1.52)	+++	NS	NS	1.33(1.16-1.53)	+++	NS	*
No	32	1.16(1.07-1.25)	+++	*		1.11(1.03-1.21)	++	***	
Study size (number of lung cancer cases)									
>100	15	1.13(1.04-1.23)	++	NS	NS	1.09(1.01-1.19)	+	***	*
50-100	15	1.38(1.19-1.61)	+++	NS		1.43(1.22-1.67)	+++	NS	
<50	14	1.28(0.99-1.67)	NS	NS		1.24(0.95-1.62)	NS	NS	
Study quality									
"Superior"	23	1.15(1.04-1.26)	++	NS	NS	1.10(1.00-1.21)	+	**	NS
"Inferior"	21	1.24(1.12-1.38)	+++	NS		1.24(1.12-1.38)	+++	*	
Study type (1)									
Prospective	5	1.22(1.01-1.48)	+	NS	NS	1.23(1.03-1.48)	+	NS	NS
Case/control	39	1.19(1.10-1.28)	+++	*		1.15(1.07-1.24)	+++	***	
Study type (2)									
Prospective	5	1.22(1.01-1.48)	+	NS	NS	1.23(1.03-1.48)	+	NS	*
Case/control:									
Healthy controls	16	1.11(1.01-1.22)	+	NS		1.06(0.97-1.16)	NS	**	
Diseased controls	20	1.32(1.16-1.51)	+++	NS		1.34(1.18-1.53)	+++	NS	
Both	2	1.02(0.57-1.84)	NS	NS		1.02(0.57-1.84)	NS	NS	
Unstated	1	2.16(1.08-4.29)	+	NS		2.16(1.08-4.29)	+	NS	

Footnotes

All meta-analyses are fixed-effects [65] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [67].

Significance codes are: +++, *** p<0.001; ++, ** p<0.01; +, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

TABLE 3 (Continued)

Meta-analyses of data for husband's smoking

	Number of studies	Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
Confounders considered									
Yes	28	1.12(1.03-1.21)	++	NS	**	1.08(1.00-1.17)	+	*	***
No	16	1.46(1.27-1.68)	+++	NS		1.46(1.27-1.69)	+++	NS	
Age adjustment/matching									
Yes	32	1.13(1.04-1.22)	++	NS	**	1.10(1.02-1.18)	+	*	***
No	12	1.53(1.30-1.81)	+++	NS		1.53(1.30-1.81)	+++	NS	
100% histological confirmation									
Yes	19	1.28(1.15-1.42)	+++	NS	NS	1.28(1.15-1.43)	+++	NS	*
No	25	1.13(1.03-1.24)	+	*		1.09(1.00-1.19)	NS	***	
Dose response data available									
Yes	28	1.23(1.13-1.34)	+++	NS	NS	1.24(1.14-1.35)	+++	NS	**
No	16	1.11(0.97-1.26)	NS	*		1.02(0.90-1.15)	NS	**	
Husband's smoking the index									
Yes	36	1.20(1.11-1.29)	+++	*	NS	1.17(1.09-1.25)	+++	***	NS
No	8	1.12(0.87-1.44)	NS	NS		1.11(0.86-1.43)	NS	NS	

Footnotes

All meta-analyses are fixed-effects [65] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [67].

Significance codes are: +++, *** p<0.001; ++, ** p<0.01; +, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

TABLE 4

Relative risk of lung cancer among lifelong nonsmoking women in relation to smoking by the husband - by histological type

Study		Relative risk (95% CI)				
Ref	Author	Adenocarcinoma/large cell		Squamous/small cell		Other/mixed
4	Trichopoulos			2.08 (1.20-3.59)	na	
8	Garfinkel 2	1.33 (0.94-1.87) 0.76 (0.51-1.13)	a l	5.00 (1.28-19.33)	sq	0.81 (0.48-1.37)
9	Lam W	2.01 (1.09-3.72)	a			
10	Wu	1.20 (0.50-3.30)	a			
12	Lee	0.41 (0.07-2.40)	alo	1.70 (0.21-13.43)	s	
13	Brownson 1	1.68 (0.39-6.90)	a			
16	Koo	1.17 (0.55-2.40)	al	1.47 (0.59-3.68)	s	
17	Lam T	2.12 (1.34-3.33)	al	1.10 (0.51-2.36)	s	1.08 (0.41-2.82)
18	Pershagen	0.80 (0.40-1.50)	alo	3.30 (1.10-11.4)	s	
26	Janerich	0.97 (0.79-1.16)	al	1.12 (0.87-1.47)	s	
27	Kalandidi	2.04 (0.98-4.24)	a	2.58 (0.88-7.57)	sl	
32	Brownson 2	1.00 (0.80-1.30)	a	0.60 (0.30-1.30) 1.20 (0.30-4.10)	sq sm	1.10 (0.70-1.70)
33	Stockwell	1.30 (0.60-2.70)	a	2.20 (0.80-5.80)	na	
35	Du	ETS exposure unassociated with cell type in cases				
36	Fontham	1.28 (1.01-1.62)	a	1.37 (0.92-2.03)	na	
43	Sun	2.86 (1.69-4.84)	a	2.06 (1.03-4.15)	s	4.87 (1.95-12.19)

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.

For study 26 the results are for sexes combined.

For study 43 the results are for exposure both at home and in the workplace.

Abbreviations for cell types are as follows:

a = adenocarcinoma l = large cell al = adenocarcinoma and large cell

alo = adenocarcinoma, large cell, and other (not squamous or small cell)

sq = squamous cell sm = small cell s = squamous and small cell

sl = squamous, small and large cell na = all except adenocarcinoma

"Other/mixed" may include other specified categories.

Relative risks presented are adjusted for covariates if adjusted data are available.

TABLE 5

Relative risk of lung cancer among lifelong nonsmoking women in relation to number of cigarettes per day smoked by husband

Study					Significance (linear trend)	
Ref	Author	Location	Groupings of cigarettes per day	Relative risk by grouping	Unexposed included	Unexposed excluded
1	Garfinkel 1	USA	None <20 20+	1.00 1.37 1.04		
4	Trichopoulos	Greece	None Ex 1-20 21+	1.00 1.95 1.95 2.54	+	
6	Hirayama	Japan	None 1-19 20+	1.00 1.43 1.74	+	
8	Garfinkel 2	USA	None <20 20-39 40+	1.00 0.84 1.08 1.99	+	+
11	Akiba	Japan	None 1-19 20-29 30+	1.0 1.3 1.5 2.1		
15	Humble	USA	None 1-20 21+	1.0 1.8 1.2		
16	Koo	Hong Kong	None 1-10 11-20 21+	1.00 2.33 1.74 1.19		
17	Lam T	Hong Kong	None 1-10 11-20 21+	1.00 2.18 1.85 2.07	+	
18	Pershagen	Sweden	None Low High	1.0 1.0 3.2		+
20	Geng	China	None 1-9 10-19 20+	1.00 1.40 1.97 2.76	+	
21	Inoue	Japan	None 1-19 20+	1.00 1.58 3.09		
24	Hole	Scotland	None 1-14 15+	1.00 0.78 1.78		
27	Kalandidi	Greece	None 1-20 21-40 41+	1.00 1.54 1.77 1.57		
34	Liu Q	China	None 1-19 20+	1.0 0.7 2.9	+	+
35	Du	China	None 1-19 20+	1.00 0.67 1.49		+
37	Cardenas	USA	None 1-19 20-39 40+	1.0 1.4 1.4 0.6		
38	Layard	USA	None <15 15-34 35+	1.00 0.54 0.76 0.00		
40	Kabat 2	USA	None 1-10 11+	1.00 0.82 1.06		
45	Wang T-J	China	None 1-9 10-19 20+	1.00 0.35 1.35 1.40		

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
For study 6 the 1-19 cigs/day group includes ex-smokers.
For study 17 the index is based not only on cigs/day, but also on pipes and duration of smoking.
Relative risks presented are adjusted for covariates if adjusted data are available.
See Appendix G for details of how the trend significances were estimated.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 6

Relative risk of lung cancer among lifelong nonsmoking women in relation to years of exposure to smoking from the husband

Study					Significance (linear trend)	
Ref	Author	Location	Groupings of years of exposure	Relative risk by grouping	Unexposed included	Unexposed excluded
5	Buffler	USA	None 1-32 33+	1.00 0.62 0.93		
10	Wu	USA	None 1-30 31+	1.0 1.2 2.0		
11	Akiba	Japan	None 1-19 20-39 40+	1.0 2.1 1.5 1.3		
14	Gao	China	1-19 20-29 30-39 40+	1.0 1.1 1.3 1.7	+	
15	Humble	USA	None 1-26 27+	1.0 1.6 2.1		
16	Koo	Hong Kong	None 1-19 20-34 35+	1.00 1.95 1.36 2.26		
20	Geng	China	None 1-19 20-39 40+	1.00 1.49 2.23 3.32	+	
23	Choi	Korea	None 1-20 21-40 41+	1.00 1.46 1.49 2.34		
26	Janerich	USA	None 1-24 25+	1.00 0.63 0.79		
27	Kalandidi	Greece	None 1-19 20-29 30-39 40+	1.00 1.26 1.33 2.01 1.88		
33	Stockwell	USA	None <22 22-39 40+	1.0 1.6 1.4 2.4		
35	Du	China	None 1-29 30+	1.00 1.35 1.08		
36	Fontham	USA	None 1-15 16-30 31+	1.00 1.10 1.33 1.23		
37	Cardenas	USA	None 1-15 16-26 27+	1.0 1.5 1.3 1.2		
43	Sun	China	None 1-34 35+	1.00 ? 0.86		
45	Wang T-J	China	0-19 20-29 30-39 40+	1.00 1.41 1.08 1.08		

Footnotes

For some studies [5,33,36] exposure also includes that from other household members.
The study author is the name of the first author in the publication from which the data were extracted; see references.
For study 26 the results are for sexes combined.
For study 43 relative risks were only presented for 35+ years exposure.
Relative risks presented are adjusted for covariates if adjusted data are available.
See Appendix G for details of how the trend significances were calculated.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 7

Relative risk of lung cancer among lifelong nonsmoking women in relation to packyears of exposure from the husband

Study					Significance (linear trend)	
Ref	Author	Location	Groupings of packyears of exposure	Relative risk by grouping	Unexposed included	Unexposed excluded
3	Correa	USA	None 1-40 41+	1.00 1.18 3.52	+	
26	Janerich	USA	None 1-24 25-49 50+	1.00 0.54 0.90 0.82		
32	Brownson 2	USA	None 1-15 16-40 41+	1.0 0.7 0.7 1.3		+
36	Fontham	USA	None 1-15 16-39 40-79 80+	1.00 1.08 1.04 1.36 1.79	+	
37	Cardenas	USA	None 1-16 17-35 36+	1.0 1.1 1.3 1.5		

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
Relative risks presented are adjusted for covarites if adjusted data are available.
See Appendix G for details of how the trend significances were calculated.
Significant ($p<0.05$) positive trends are indicated by +.

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TABLE 8

Results of misclassification corrected meta-analyses of lung cancer risk associated with husband's smoking

Misclassification Rates (%)				Meta-analysis relative risks (95% CI)					
				Including Greek and Russian Studies				Excluding Greek and Russian Studies	
In USA & Europe	In Asia	Concordance Ratio	Model	USA (17 studies)	Europe (8 studies)	Asia (19 studies)	Total (44 studies)	Europe (5 studies)	Total (41 studies)
0.0	**0.0**	**-**	**-**	**1.12(1.01-1.24)**	**1.52(1.22-1.90)**	**1.20(1.08-1.34)**	**1.19(1.11-1.28)**	**1.19(0.83-1.72)**	**1.16(1.08-1.25)**
1.0	1.0	3.0	Mult	1.08(0.97-1.19)	1.50(1.20-1.88)	1.19(1.07-1.33)	1.17(1.09-1.25)	1.16(0.80-1.69)	1.13(1.05-1.22)
2.5	**2.5**	**3.0**	**Mult**	**1.01(0.90-1.12)**	**1.48(1.18-1.86)**	**1.18(1.06-1.32)**	**1.13(1.05-1.21)**	**1.12(0.77-1.63)**	**1.09(1.01-1.18)**
4.0	4.0	3.0	Mult	0.93(0.84-1.04)	1.46(1.16-1.83)	1.17(1.05-1.31)	1.09(1.01-1.17)	1.07(0.73-1.58)	1.05(0.97-1.13)
2.5	5.0	3.0	Mult	1.01(0.90-1.12)	1.48(1.18-1.86)	1.16(1.04-1.30)	1.12(1.04-1.20)	1.12(0.77-1.63)	1.08(1.00-1.17)
2.5	**10.0**	**3.0**	**Mult**	**1.01(0.90-1.12)**	**1.48(1.18-1.86)**	**1.12(1.00-1.25)**	**1.10(1.02-1.18)**	**1.12(0.77-1.63)**	**1.06(0.99-1.15)**
2.5	20.0	3.0	Mult	1.01(0.90-1.12)	1.48(1.18-1.86)	1.02(0.90-1.14)	1.05(0.98-1.14)	1.12(0.77-1.63)	1.01(0.94-1.10)
2.5	2.5	2.0	Mult	1.04(0.93-1.16)	1.50(1.19-1.88)	1.19(1.07-1.32)	1.15(1.07-1.23)	1.14(0.78-1.67)	1.11(1.03-1.20)
		4.0	Mult	0.98(0.88-1.10)	1.47(1.18-1.85)	1.18(1.06-1.31)	1.11(1.04-1.20)	1.10(0.76-1.61)	1.08(1.00-1.16)
		2.0	Add	1.04(0.94-1.16)	1.50(1.20-1.89)	1.19(1.07-1.33)	1.15(1.07-1.24)	1.15(0.78-1.68)	1.12(1.04-1.20)
		3.0	Add	1.00(0.90-1.12)	1.49(1.19-1.86)	1.19(1.06-1.32)	1.13(1.05-1.21)	1.12(0.77-1.64)	1.09(1.01-1.18)
		4.0	Add	0.98(0.88-1.09)	1.48(1.18-1.85)	1.18(1.06-1.32)	1.11(1.04-1.20)	1.11(0.76-1.61)	1.08(1.00-1.16)
2.5	10.0	2.0	Mult	1.04(0.93-1.16)	1.50(1.19-1.88)	1.15(1.03-1.28)	1.13(1.05-1.22)	1.14(0.78-1.67)	1.09(1.01-1.18)
		4.0	Mult	0.98(0.88-1.10)	1.47(1.18-1.85)	1.11(0.99-1.24)	1.08(1.00-1.16)	1.10(0.76-1.61)	1.04(0.97-1.13)
		2.0	Add	1.04(0.94-1.16)	1.50(1.20-1.89)	1.16(1.03-1.29)	1.13(1.05-1.22)	1.15(0.78-1.68)	1.10(1.02-1.19)
		3.0	Add	1.00(0.90-1.12)	1.49(1.19-1.86)	1.13(1.01-1.26)	1.10(1.02-1.18)	1.12(0.77-1.64)	1.06(0.99-1.15)
		4.0	Add	0.98(0.88-1.09)	1.48(1.18-1.85)	1.11(0.99-1.24)	1.08(1.00-1.16)	1.11(0.76-1.61)	1.04(0.97-1.13)

Footnotes

The table shows the misclassification corrected meta-analysis relative risks by continent and overall depending on various assumptions concerning the misclassification rate, the between spouse smoking habit concordance ratio and the model assumed.
(Mult = Multiplicative; Add = Additive).

TABLE 9

Effect of misclassification correction on relative risks in studies of over 100 lung cancer cases

Study		Misclassification rate (%)						
Ref	Author	0	1	2.5	4	5	10	20
1	Garfinkel 1	1.17 (0.85-1.61)	1.16	1.15 (0.83-1.59)	1.14			
6	Hirayama	1.38 (0.97-1.98)	1.38	1.37	1.37	1.36	1.34 (0.93-1.92)	1.27
8	Garfinkel 2	1.23 (0.81-1.87)	1.21	1.16 (0.76-1.78)	1.12			
14	Gao	1.19 (0.82-1.73)	1.18	1.17	1.17	1.16	1.12 (0.77-1.65)	1.03
17	Lam T	1.65 (1.16-2.35)	1.63	1.61	1.59	1.58	1.50 (1.03-2.17)	1.30
26	Janerich	0.75 (0.47-1.20)	0.72	0.66 (0.40-1.07)	0.60			
28	Sobue	1.06 (0.74-1.52)	1.06	1.05	1.04	1.04	1.01 (0.69-1.46)	0.94
29	Wu-Williams	0.79 (0.62-1.02)	0.79	0.78	0.77	0.76	0.72 (0.55-0.94)	0.63
32	Brownson 2	0.97 (0.78-1.21)	0.92	0.84 (0.67-1.07)	0.76			
33	Stockwell	1.60 (0.80-3.19)	1.53	1.43 (0.70-2.93)	1.32			
36	Fontham	1.26 (1.04-1.54)	1.21	1.12 (0.91-1.37)	1.02			
37	Cardenas	1.10 (0.79-1.53)	1.05	0.98 (0.69-1.39)	0.91			
39	Zaridze	1.66 (1.12-2.45)	1.65	1.64 (1.11-2.42)	1.63			
43	Sun	1.16 (0.80-1.68)	1.15	1.13	1.12	1.11	1.05 (0.71-1.55)	0.89
45	Wang T-J	1.11 (0.67-1.84)	1.10	1.08	1.07	1.06	1.00 (0.59-1.70)	0.86
46	Schwartz	1.18 (0.77-1.82)	1.13	1.05 (0.67-1.64)	0.97			

Footnote

The table shows the relative risks for varying smoking habit misclassification rates assuming a multiplicative model and a between spouse smoking habit concordance ratio of 3.0.

The 95% CI is shown beneath the relative risk for all studies for 0% misclassification, and also for US and European studies for 2.5% misclassification, and for Asian studies for 10% misclassification rates.

TABLE 10

Relative risk of lung cancer among lifelong nonsmoking men in relation to smoking by the wife

Study		Number of lung cancer cases	Unadjusted data		Covariate adjusted data	
Ref	Author		Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
3	Correa	8	1.97(0.38-10.32)			
5	Buffler	11	0.51(0.14-1.79)			
6	Hirayama	64	2.34(1.07-5.13)+	2.25(1.19-4.22) +		
7	Kabat 1	12	1.00(0.20-5.07)			
11	Akiba	19	2.10(0.51-8.61)	1.80(0.40-7.00)		
12	Lee	15	1.31(0.38-4.52)	1.30(0.38-4.39)		
15	Humble	8	4.19(0.95-18.42)		4.82(0.63-36.56)	
23	Choi	13	2.73(0.49-15.21)			
24	Hole	3	3.52(0.32-38.65)			
26	Janerich	44	0.75(0.31-1.78)			
31	Joeckel	9	2.68(0.58-12.36)			
37	Cardenas	101	0.90(0.56-1.44)	0.90(0.60-1.40)		
38	Layard	21	1.46(0.56-3.80)	1.47(0.55-3.94)		
40	Kabat 2	39	1.63(0.69-3.85)	1.60(0.67-3.82)		
46	Schwartz	72	1.18(0.63-2.20)	1.10(0.60-2.03)		

Footnotes

In two studies (5,24) the index of exposure is not based on husband's smoking, but on the nearest equivalent index (see Table 14).

The study author is the name of the first author in the publication from which the data were extracted; see references.

For one study (37) the data in the unadjusted column are adjusted for age, and in the adjusted column are adjusted for age and other risk factors.

See Appendix B for details of how the data were extracted from the source publication.

See Appendix C for the covariates considered in the adjusted analyses.

Significant ($p<0.05$) positive relative risks are indicated by +

TABLE 11

Meta-analyses of data for wife's smoking

	Number of studies		Unadjusted data: Relative risk (95% CI)	Unadjusted data: Significance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between		Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Significance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
All studies	15		1.28(1.00-1.64)	NS	NS			1.24(0.98-1.57)	NS	NS	
	15	R	1.31(1.00-1.86)	+	NS		R	1.29(0.98-1.80)	NS	NS	
Continent											
USA	9		1.09(0.82-1.45)	NS	NS	NS		1.04(0.79-1.36)	NS	NS	*
Europe	3		1.92(0.78-4.69)	NS	NS			1.90(0.78-4.62)	NS	NS	
Asia	3		2.34(1.24-4.42)	++	NS			2.22(1.28-3.84)	++	NS	

Footnotes

All meta-analyses are fixed-effects [65] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [67].

Significance codes are: +++, *** p<0.001; ++, ** p<0.01; +, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

TABLE 12

Relative risk of lung cancer among lifelong nonsmoking men in relation to extent of exposure to smoking from the wife

Study					
Ref	Author	Location	Groupings	Relative risk by grouping	Significance (trend)
Cigarettes per day smoked by the wife					
37	Cardenas	USA	None 1-19 20-39 40+	1.0 2.0 0.0 0.0	
38	Layard	USA	None <15 15-34 35+	1.00 2.04 1.15 0.00	
40	Kabat 2	USA	None 1-10 11+	1.00 0.74 7.48	?
Years of exposure to smoking from the wife					
5	Buffler	USA	None <33 33+	1.00 0.40 1.56	
37	Cardenas	USA	None 1-15 16-26 27+	1.00 0.4 1.2 0.7	
Pack years of exposure from the wife					
3	Correa	USA	None 1-40 41+	1.0 2.57 0.00	
37	Cardenas	USA	None 1-8 9-22 23+	1.0 0.4 1.4 0.5	

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
For study 5 exposure also includes that from other household members.
For study 40 the relative risk of 7.48 was significant, but it was not clear whether the trend was.
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 13

Meta-analyses of data for spousal smoking

	Number of studies		Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
All studies	59		1.20(1.12-1.28)	+++	NS		1.17(1.09-1.25)	+++	**	
	59	R	1.24(1.13-1.36)	+++	*		1.25(1.13-1.38)	+++	***	
Continent										
USA	26		1.12(1.02-1.23)	+	NS	*	1.11(1.01-1.22)	+	NS	**
Europe	11		1.54(1.24-1.91)	+++	NS		1.64(1.31-2.05)	+++	NS	
Asia	22		1.22(1.10-1.36)	+++	*		1.16(1.05-1.28)	++	***	
	22	R	1.30(1.13-1.55)	+++	**		1.32(1.12-1.58)	++	***	
Publication date										
1981-86	18		1.31(1.13-1.52)	+++	NS	***	1.32(1.14-1.52)	+++	NS	***
1987-89	16		1.47(1.24-1.73)	+++	NS		1.48(1.25-1.76)	+++	NS	
1990-92	10		0.96(0.84-1.09)	NS	NS		0.92(0.81-1.04)	NS	**	
1993-96	15		1.22(1.09-1.36)	+++	NS		1.21(1.07-1.35)	++	NS	

Footnotes

All meta-analyses are fixed-effects [65] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [67].

Significance codes are: +++, *** p<0.001; ++, ** p<0.01; +, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

TABLE 14

Relative risk of lung cancer among lifelong nonsmoking women in relation to smoking in the household

Study Ref	Author	Location	Index of exposure	Relative risk (95% CI)	Significance
Already included in Table 2					
2	Chan	Hong Kong	Exposed at home or at work	0.75(0.43-1.30)	
5	Buffler	USA	Household member smokes regularly	0.80(0.34-1.90)	
13	Brownson 1	USA	Presence of persons smoking 4+ hours/day	1.68(0.39-6.90)	
24	Hole	Scotland	Household member ever smoked	1.89(0.22-16.12)	
25	Svensson	Sweden	Exposed at home or at work	1.26(0.57-2.81)	
30	Liu Z	China	Smoker in household	0.77(0.30-1.96)	
44	Wang S-Y	China	Exposed at home or at work	2.53(1.26-5.10)	+
46	Schwartz	USA	Exposed at home	1.10(0.72-1.68)	
Not included in Table 2					
7	Kabat 1	USA	Regular exposure to family member	0.92(0.40-2.08)	
8	Garfinkel 2	USA	Exposure at home in last 5 years Exposure at home in last 25 years	1.22(0.78-1.93) 1.15(0.74-1.78)	
12	Lee	England	Exposure at home	0.80(0.37-1.71)	
14	Gao	China	Lived with smoker	0.90(0.60-1.40)	
16	Koo	Hong Kong	Cohabitant smokes in subject's presence	1.26(0.71-2.23)	
22	Shimizu	Japan	Father smokes at home Mother smokes at home Father-in-law smokes at home Mother-in-law smokes at home Child smokes at home Sibling smokes at home	1.1(0.69-1.84) 4.0(1.31-11.9) 3.2(1.50-6.80) 0.8(0.30-2.25) 0.8(0.19-3.05) 0.8(0.46-1.35)	 + +
27	Kalandidi	Greece	Household member other than spouse smokes	1.41(0.70-2.86)	
28	Sobue	Japan	Household member other than spouse smokes	1.50(1.01-2.22)	+
29	Wu-Williams	China	Any cohabitant smokes Father smokes Mother smokes	0.78(0.56-1.10) 1.09(0.84-1.40) 0.85(0.65-1.12)	
32	Brownson 2	USA	All household members	1.10(0.80-1.30)	
33	Stockwell	USA	Any household exposure Mother Father Siblings and others	1.61(1.07-2.43) 1.6(0.6-4.3) 1.2(0.6-2.3) 1.7(0.8-3.9)	+
36	Fontham	USA	Household exposure	1.23(0.96-1.57)	
39	Zaridze	Russia	Other family members	1.08(0.67-1.74)	
40	Kabat 2	USA	Exposed in adulthood at home	0.95(0.53-1.67)	

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
In some studies [16, 22, 29, 33, 39] exposure may have occurred either as an adult or a child.
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive relative risks are indicated by +.

TABLE 15

Relative risk of lung cancer among lifelong nonsmoking women in relation to extent of ETS exposure in the household

Study Ref	Author	Location	Aspect/ Grouping	Relative risk by grouping	Significance (trend)
11	Akiba	Japan	Recency of exposure (years ago) None >10 ≤10	1.0 1.3 1.8	
12	Lee	UK	Passive smoke exposure index Not at all Little Average/A lot	1.00 0.92 0.81	
16	Koo	Hong Kong	Numbers of smoking cohabitants 0 1 2+	1.00 1.73 1.35	
			Hours/day exposed 0 <1 <2 2+	1.00 1.05 4.10 1.00	
			Total hours exposed (hundreds) 0 1-100 101-200 201+	1.00 1.68 2.28 1.42	
			Cigarettes/day 0 1-10 11-20 21+	1.00 1.83 2.56 1.21	
27	Kalandidi	Greece	Household exposure to other than spouse None Low Medium High	1.00 1.93 1.54 0.98	
32	Brownson 2	USA	Cigarette pack-years 0 1-15 16-40 41+	1.0 0.9 0.9 1.3	
			Pack years x hours/day 0 1-50 51-175 176+	1.0 0.9 0.9 1.3	
37	Cardenas	USA	Hours exposed at home 0 1-3 4-5 6+	1.0 0.4 0.7 1.3	
40	Kabat 2	USA	No. of smokers in household in adulthood 0 1 2+	1.00 0.96 0.94	
43	Sun	China	Lifetime exposure to ETS in the home "Significantly associated"		+

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 12 relative risks for men are 1.00, 1.22, 1.11 (trend not significant).
In study 37 relative risks for men are 1.0, 0.7, 0.0, 0.5 (trend not significant).
In study 40 relative risks for men are 1.00, 0.64, 4.15 (trend not significant).
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive relative risks are indicated by +.

TABLE 16

Relative risk of lung cancer among lifelong nonsmokers in relation to ETS exposure in the workplace

Study			Unadjusted data		Covariate adjusted data	
Ref	Author	Sex	Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
7	Kabat 1	Females	0.68(0.32-1.47)			
		Males	3.27(1.01-10.62)	+		
8	Garfinkel 2	Females	0.93(0.55-1.55)			
10	Wu	Females			1.30(0.50-3.30)	
12	Lee	Females	0.63(0.17-2.33)			
		Males	1.61(0.39-6.60)			
16	Koo	Females	1.19(0.48-2.95)			
22	Shimizu	Females	1.18(0.70-2.01)			
26	Janerich	Combined	0.91(0.80-1.04)			
27	Kalandidi	Females	1.70(0.69-4.18)			
29	Wu-Williams	Females	1.22(0.95-1.57)		1.10(0.90-1.60)	
32	Brownson 2	Females			0.79(0.61-1.03)	
33	Stockwell	Females	No association		No association	
36	Fontham	Females	1.12(0.91-1.36)		1.39(1.11-1.74)	+
37	Cardenas	Females	No association		No association	
		Males	No association		No association	
39	Zaridze	Females	1.18(0.71-1.96)		1.23(0.74-2.06)	
40	Kabat 2	Females	1.15(0.62-2.13)			
		Males	1.02(0.50-2.09)			
43	Sun	Females			1.38(0.94-2.04)	
45	Wang T-J	Females	0.89(0.46-1.73)			
46	Schwartz	Females	1.35(0.89-2.04)		1.50(0.99-2.26)	
		Males	1.35(0.74-2.45)		1.50(0.75-3.01)	

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 26 the risk is per 150 person-years of exposure.
In study 27 the risk is for some vs minimal exposure.
See Appendix B for details of how the data were extracted from the source publication.
See Appendix C for the covariates considered in the adjusted analyses.
Significant ($p<0.05$) positive relative risks are indicated by +.

TABLE 17

Relative risk of lung cancer among lifelong nonsmoking women in relation to extent of ETS exposure in the workplace

Study					
Ref	Author	Location	Aspect/ Grouping	Relative risk by grouping	Significance (trend)
12	Lee	UK	Passive smoke exposure index Not at all Little Average/A lot	1.00 1.18 0.00	
32	Brownson 2	USA	Quartiles of workplace exposure 1 2 3 4	1.0 ? ? 1.2	
36	Fontham	USA	Years of occupational exposure 0 1-15 16-30 31+	1.00 1.30 1.40 1.86	+
37	Cardenas	USA	Hours exposed at work 0 1 2-6 7+	1.0 0.9 1.1 1.0	
40	Kabat 2	USA	Smoker Low Intermediate High	1.00 0.94 1.35	

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 12 relative risks for men are 1.00, 3.24, 0.46 (trend not significant).
In study 32 results only cited for highest quartile of workplace exposure.
In study 37 relative risks for men are 1.0 0.7 1.0 1.8 (trend not significant).
In study 40 relative risks for men are 1.00, 1.13, 1.21 (trend not significant).
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 18

Relative risk of lung cancer among lifelong nonsmokers in relation to ETS exposure in childhood

Study			Unadjusted data		Covariate adjusted data	
Ref	Author	Sex	Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
3	Correa	Combined	No association			
8	Garfinkel 2	Females	0.91(0.74-1.12)			
10	Wu	Females			0.60(0.20-1.70)	
11	Akiba	Combined	No association		No association	
14	Gao	Females			1.10(0.70-1.70)	
16	Koo	Females	0.55(0.17-1.77)			
18	Pershagen	Females			1.00(0.40-2.30)	
25	Svensson	Females	3.09(0.68-14.06)		3.30(0.50-18.80)	
26	Janerich	Combined	1.30(0.85-2.00)			
28	Sobue	Females	1.42(0.80-2.51)		1.28(0.71-2.31)	
29	Wu-Williams	Females	0.85(0.65-1.12)			
32	Brownson 2	Females	0.74(0.57-0.95)	–	0.80(0.60-1.10)	
33	Stockwell	Females			1.70(1.00-2.90)	
36	Fontham	Females	0.88(0.72-1.07)		0.89(0.72-1.10)	
39	Zaridze	Females	0.97(0.66-1.42)		0.98(0.66-1.45)	
40	Kabat 2	Females Males	1.63(0.91-2.92) 0.90(0.43-1.89)			
43	Sun	Females			2.29(1.56-3.37)	+
45	Wang T-J	Females	0.91(0.56-1.48)			

Footnotes

Index of exposure based on any household exposure if available or mother if not.

The study author is the name of the first author in the publication from which the data were extracted; see references.

See Appendix B for details of how the data were extracted from the source publication.

See Appendix C for the covariates considered in the adjusted analyses.

Significant ($p<0.05$) positive relative risks are indicated by +, with significant ($p<0.05$) negative relative risks indicated by –.

TABLE 19

Relative risk of lung cancer among lifelong nonsmoking women in relation to extent of ETS exposure in childhood

Study					
Ref	Author	Location	Aspect/ Grouping	Relative risk by grouping	Significance (trend)
26	Janerich	USA	Smoker-years of exposure in childhood and adolescence		
			0 1-24 25+	1.00 1.09 2.07	+
32	Brownson 2	USA	Cigarette pack-years (household members)		
			0 1-15 16-25 26+	1.0 0.7 0.6 0.7	
			Cigarette pack-years (parents only)		
			0 1-15 16-25 26+	1.0 0.5 0.5 0.8	
			Passive smoke in childhood		
			0 Light Moderate Heavy	1.0 ? 1.7 2.4	+
33	Stockwell	USA	Smoke-years of exposure in childhood and adolescence		
			0 <18 18-21 22+	1.0 1.6 1.1 2.4	
36	Fontham	USA	Smoke years of household exposure		
			0 1-17 18+	1.00 0.99 0.88	
40	Kabat 2	USA	No. of smokers in household in childhood		
			0 1 2+	1.00 1.75 1.28	
			Smoker-years in childhood		
			Low Intermediate High	1.00 1.73 2.19	+

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 32 results only cited for moderate and heavy exposure to passive smoke in childhood.
In study 40 relative risks for men are 1.00, 0.93, 0.87 and 1.00, 0.95, 1.39 (trends not significant) for the two indices of extent of exposure.
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 20

Relative risk of lung cancer among lifelong nonsmokers in relation to ETS exposure in social situations

Study				Unadjusted data		Covariate adjusted data	
Ref	Author	Index of Exposure	Sex	Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
8	Garfinkel 2	Exposure in areas other than home or work in last 25 years	Females	1.42(0.75-2.70)			
12	Lee	Exposure during leisure	Females Males	0.61(0.29-1.28) 1.55(0.40-6.02)			
26	Janerich	Social exposure	Combined	0.59(0.43-0.81)	–		
33	Stockwell	Social exposure	Female	No association		No association	
36	Fontham	Social exposure	Females	1.41(1.14-1.75)	+	1.50(1.19-1.89)	+
40	Kabat 2	Social exposure	Females Males	1.22(0.69-2.15) 1.39(0.67-2.86)			

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 26 the risk is per increase of 20 in cumulative score.
See Appendix B for details of how the data were extracted from the source publication.
See Appendix C for the covariates considered in the adjusted analyses.
Significant ($p<0.05$) positive relative risks indicated by +, with significant ($p<0.05$) negative relative risks indicated by –.

TABLE 21

Relative risk of lung cancer among lifelong nonsmoking women in relation to extent of social exposure to ETS

Study					
Ref	Author	Location	Aspect/ Grouping	Relative risk by grouping	Significance (trend)
12	Lee	UK	Passive smoke exposure index Not at all Little Average/A lot	1.00 1.05 0.18	–
36	Fontham	USA	Years of exposure 0 1-15 16-30 31+	1.00 1.45 1.59 1.54	+
37	Cardenas	USA	Hours exposed other than home or work 0 1 2 3+	1.0 1.0 0.8 1.1	

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
For study 12 relative risks for men are 1.00, 1.12, 3.18 (trend not significant).
For study 37 relative risks for men are 1.0, 0.5, 0.7 1.1 (trend not significant).
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive trends are indicated by + with significant ($p<0.05$) negative trends indicated by –.

TABLE 22

Relative risk of lung cancer among lifelong nonsmokers in relation to total ETS exposure

Study				Unadjusted data		Covariate adjusted data	
Ref	Author	Index of exposure	Sex	Relative risk (95% CI)	Significance	Relative risk (95% CI)	Significance
8	Garfinkel 2 of others in 25	Exposed to smoke years before diagnosis	Females	1.12(0.74-1.70)			
9	Lam W	Exposed at home or at work	Females	2.51(1.35-4.67)	+		
12	Lee	Combined index score 2 or more	Females Males	0.46(0.15-1.40) 3.47(0.42-28.72)			
14	Gao	Exposure in adult life	Females			0.90(0.60-1.40)	
16	Koo	Any exposure	Females	1.24(0.67-2.27)			
25	Svensson	Any lifetime exposure	Females	0.97(0.39-2.41)			
26	Janerich	Any exposure in lifetime	Combined	1.04(0.61-1.77)			
31	Joeckel	Any source	Females Males	1.63(0.59-4.47) 6.77(1.33-34.33)	 +		
33	Stockwell	>40 smoke years lifetime household exposure	Females			2.30(1.10-4.60)	+
36	Fontham	Any exposure in adulthood	Females	1.16(0.82-1.65)			
37	Cardenas	Any reported exposure	Females Males	0.90(0.70-1.20) 0.60(0.40-1.00)	 -		
40	Kabat 2	Exposure in adulthood high	Females Males			1.14(0.56-2.33) 1.50(0.46-4.89)	
41	de Waard	Urine cotinine >9.2 ng/mg	Females	2.57(0.84-7.85)			
42	Shen	>20 cigs/day	Females	0.85(0.26-2.74)			
43	Sun	Exposed at home and work	Females			2.92(1.89-4.49)	+

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.

In study 42 it is unknown whether the relative risk is adjusted or not.

See Appendix B for details of how the data were extracted from the source publication.

See Appendix C for the covariates considered in the adjusted analyses.

Significant ($p<0.05$) positive relative risks are indicated by +, with significant ($p<0.05$) negative relative risks indicated by −.

TABLE 23

Relative risk of lung cancer among lifelong nonsmoking women in relation to extent of total ETS exposure

Study					
Ref	Author	Location	Aspect/ grouping	Relative risk by grouping	Significance (trend)
8	Garfinkel 2	USA	Hours/day smoke of others last 5 years 0 1-2 3-6 7+	1.00 1.59 1.39 0.94	
			Hours/day smoke of others last 25 years 0 1-2 3-6 7+	1.00 0.77 1.34 1.14	
12	Lee	UK	Combined exposure score 0-1 2-4 5-12	1.00 0.63 0.00	
16	Koo	Hong Kong	Period in life exposed None Child Adult Both	1.00 2.07 1.68 0.64	
25	Svensson	Sweden	Lifetime exposure None Child or adult Both	1.00 1.4 1.9	
			Adult exposure None Home or work Both	1.0 1.2 2.1	
26	Janerich	USA	Adult smoke-years of exposure 0 1-24 25-49 50-74 75+	1.00 0.64 0.81 1.00 1.11	
			Lifetime smoke-years of exposure 0 1-24 25-49 50-74 75-99 100+	1.00 0.78 0.80 1.19 1.80 1.13	
31	Joeckel	Germany	Any source No Average High	1.00 2.12 3.43	
33	Stockwell	USA	Smoke-years: all lifetime household exposure 0 <22 22-39 40+	1.0 1.3 1.4 2.3	+
36	Fontham	USA	Adult smoke-years of exposure 0 1-11 12-28 29-47 48+	1.00 0.82 1.12 1.35 1.74	+
37	Cardenas	USA	Hours of exposure 0 1-2 3-5 6+	1.0 0.8 0.7 1.1	
40	Kabat 2	USA	Smoker-years in adulthood Low Intermediate High	1.00 1.30 1.14	
41	de Waard	Holland	Urinary cotinine (ng/mg creatinine) <9.2 9.2-23.4 23.4-100	1.0 2.7 2.4	
43	Sun	China	Years of exposure "Significantly associated"		+

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
For study 12 relative risks for men are 1.00, 4.34, 3.20 (trend not significant).
For study 37 relative risks for men are 1.0, 0.6, 1.0, 1.3 (trend not significant).
For study 40 relative risks for men are 1.00, 1.98, 1.50 (trend not significant).
Relative risks presented are adjusted for covariates if adjusted data are available.
Significant ($p<0.05$) positive trends are indicated by +.

TABLE 24

Re-analysis of data in Fontham study on joint effect of childhood and adulthood ETS exposure

Group	Childhood ETS exposure	Adulthood ETS exposure	Controls	Cases	Relative risks (95% CI) Varying base	Relative risks (95% CI) Common base
1	No	No	71	23	1.00 (base 1)	1.00 (base)
2	No	Yes	364	118	1.00 (0.60-1.67)	1.00 (0.60-1.67)
3	Yes	No	44	5	1.00 (base 2)	0.35 (0.12-0.99)
4	Yes	Yes	724	235	2.86 (1.12-7.29)	1.00 (0.61-1.64)
					Fitted cases	Standardised residuals
1	No	No	71	23	18.90	+1.055
2a	No	1-11	90	23	23.53	−0.123
2b	No	12-28	97	28	28.21	−0.045
2c	No	29-47	97	36	33.19	+0.562
2d	No	48+	80	31	31.85	−0.179
3	Yes	No	44	5	9.85	−1.730
4a	Yes	1-11	137	29	34.57	−1.064
4b	Yes	12-28	201	69	60.93	+1.174
4c	Yes	29-47	204	67	67.64	−0.089
4d	Yes	48+	182	70	72.32	−0.323

Footnotes

The source of the data is ref 36, Table 8; Crude data and data for self-respondents only have been selected - patterns of response were similar using covariate adjusted data and data for all respondents.

Adulthood ETS exposure is in smoke-years.

Fitted cases were estimated using the General Linear Interactive Modelling Program (with a logit link) and a model in which risk depended only on adulthood exposure (using scores of 0, 6, 20, 38 and 64 for the 5 dose groups). The model was significant (χ^2 for fit = 7.70 on 1 d.f., $p<0.01$) with a nonsignificant residual (χ^2 = 7.55 on 8 d.f.). There was no evidence of non-linearity (χ^2 = 1.93 on 3 d.f.) Adding in childhood exposure (χ^2 = 0.43 on 1 d.f.) and its interaction with adulthood exposure (χ^2 = 0.42 on 1 d.f.) did not improve the fit.

Standardized residuals are expressed as normal deviates.

TABLE 25

Meta-analyses of data for five indices of ETS exposure

Index of ETS exposure	Sex	Number of estimates	Unadjusted data: Relative risk (95% CI)	Unadjusted data: Significance	Data adjusted for covariates: Relative risk (95% CI)	Data adjusted for covariates: Significance
Husband's smoking	F	44	1.19(1.11-1.28)	+++	1.16(1.09-1.25)	+++
Wife's smoking	M	15	1.28(1.00-1.64)	NS	1.24(0.98-1.57)	NS
Workplace	M+F	20	1.03(0.95-1.11)	NS	1.05(0.96-1.14)	NS
Childhood	M+F	17	0.99(0.90-1.08)	NS	1.01(0.92-1.11)	NS
Social	M+F	7	1.09(0.94-1.28)	NS	1.10(0.94-1.30)	NS

Footnotes

All meta-analyses are fixed effects [65] and take no account of potential bias from misclassification of smoking habits, or other sources of bias described in sections 13.5-13.9.

Significance codes are: +++, *** p<0.001; ++, ** p<0.01; +, * p<0.05; and NS (not significant) p>0.05.

TABLE 26

The Health and Lifestyle Survey
Association between cotinine level in saliva and risk factor prevalence (%) in lifelong never smokers

		Cotinine level in saliva (ng/mg)						
		0.0-0.5	0.6-1.0	1.1-2.0	2.1-5.0	5.1-30.0	Trend	
Risk factor	%	%	%	%	%	Chisquared	p	
Significant positive associations								
Social class IIIM or below		37.3	41.6	53.3	54.1	63.1	43.4	<0.001
No educational qualifications		28.2	30.2	39.0	38.1	55.2	39.8	<0.001
Extroversion (score >11)		32.1	42.5	43.2	49.5	56.1	36.0	<0.001
"Risky" occupation		21.9	21.2	26.5	33.2	44.3	20.0	<0.001
Income <£250 per week		45.4	43.9	49.5	54.0	58.9	19.8	<0.001
Fried food (score 8+)		15.3	20.0	20.7	24.0	28.6	16.4	<0.001
Mildly overweight or obese		51.0	55.7	58.0	63.1	65.2	12.9	<0.001
Breakfast cereal 1/wk or less		25.1	28.2	30.4	29.5	38.2	11.3	<0.001
Alcohol consumption moderate+	18.4	23.3	23.1	36.1	28.8	10.1	<0.01	
Do nothing to keep healthy		28.2	29.8	28.5	35.8	43.2	9.1	<0.01
Fruits (score <8)		26.3	23.1	32.0	30.4	38.5	9.0	<0.01
Don't use low fat/PU spread		21.7	20.7	20.4	28.3	37.6	8.8	<0.01
2 hours + before first meal		14.6	17.3	18.9	21.6	15.7	8.6	<0.01
Mother dead		44.5	41.5	45.7	46.8	59.6	6.6	<0.05
Sugar in tea or coffee		35.7	35.7	39.8	37.1	50.2	5.9	<0.05
Bread (4+slices per day)		45.4	42.4	47.1	49.7	51.1	4.2	<0.05
Significant negative association								
Sweet foods (score >12)		59.7	59.3	54.9	49.8	47.2	7.4	<0.01
Number of subjects		511	278	241	221	93		

Footnotes
Percentages adjusted for sex and age.
Significance of trend based on Fry-Lee stratified rank test [94]using full risk factor distribution.
Numbers of subjects are less than stated for some analyses due to missing data on risk factors.
Risky occupation analysis restricted to those aged <60.
PU = Polyunsaturated fat.
For definition of risk factors see ref 70.
Risk factors showing no significant association were: father dead; divorced, separated or widowed; household size 3+; not in paid employment; do not get enough exercise; had depression/nervous illness; sleeps less than 7 hours; vegetables (score <8); salads (score <6); tea (7+ cups per day); coffee (7+ cups per day); underweight; neuroticism (score <9); and type A personality.

TABLE 27

Health Survey for England 1993
Association between cotinine level in serum and risk factor prevalence (%)
in lifelong never smokers

		Cotinine level in serum (ng/mg)						
		0.0-0.2	0.3-0.5	0.6-1.0	1.1-2.0	2.1-20.0	Trend	
Risk factor	%	%	%	%	%	Chisquared	p	
Significant positive associations								
Social class IIIM or below		27.2	31.9	39.3	44.7	54.1	48.3	< 0.001
No educational qualifications		22.8	26.9	23.8	33.8	38.0	45.3	< 0.001
Alcohol consumption moderate +22.0		23.3	34.9	34.2	39.7		29.9< 0.001	
Eats vegetables or salad < once a day		26.8	28.8	28.9	33.2	38.5	19.6	< 0.001
Eats fruit < once a day		45.1	41.0	43.0	45.5	59.6	18.6	< 0.001
Low control at work		17.9	20.2	23.8	27.8	32.7	16.7	< 0.001
Divorced, separated or widowed		10.9	14.0	11.7	13.6	16.8	13.6	< 0.001
Mildly overweight or obese		54.0	54.9	57.8	62.3	65.1	12.3	< 0.001
Not married (or cohabiting)		32.3	34.8	32.3	35.4	44.1	9.2	< 0.01
Salt in food (score 5+)		36.8	39.3	40.6	38.0	46.7	6.9	< 0.01
Mother dead		38.8	41.3	43.0	48.3	43.7	6.3	< 0.05
Sugar in hot drinks		39.0	42.5	34.9	45.3	48.2	4.0	< 0.05
Significant negative association								
Sweet foods (score > 10)		52.3	49.9	47.1	48.3	42.3	5.8	< 0.05
Number of subjects		374	509	406	279	211		

Footnotes
Percentages adjusted for sex and age.
Significance of trend based on Fry-Lee stratified rank test [94]using full risk factor distribution.
Numbers of subjects are less than stated for some analyses due to missing data on risk factors.
Risk factors defined as comparably as possible to Table 26.
Risk factors showing no significant association were: father dead; household size 3+; not in work; out of work; inactive or lightly active; has mental illness/handicap; bread (> 1 times per day); drinks tea; drinks coffee ;usual spread eaten butter/block margarine or soft margarine; underweight; eats fried food; life worse than usual; has a long-standing illness; speed/pressure at work high.

TABLE 28

Selection by Trédaniel et al [56] of inappropriate estimates of relative risk of lung cancer associated with spousal smoking

Study		Appropriate estimate		Inappropriate estimate	
Ref	Author	Index of exposure	Relative Risk	Index of exposure	Relative risk
14	Gao	Lived 20+ years with smoking husband	1.19	Lived 40+ years with smoking husband	1.70
15	Humble	Husband smoked cigarettes and/or pipe/cigar	2.20	Spouse smoked cigarettes and/or pipe/cigar	2.60
22	Shimizu	Husband a smoker	1.08	Mother a smoker Husband's father a smoker	4.00 3.20
25	Svenson	Exposed at home as adult	1.26	Exposed at home and at work as adult	2.10
26	Janerich	Ever had spouse who smoked	0.75	75+ smoker years adult ETS exposure	1.11
28	Sobue	Husband smoked	1.13	Other household members smoked in adulthood	1.50
32	Brownson 2	Husband ever smoked	1.00	Heavy exposure to passive smoke	1.80
34	Liu Q	Husband smoked	1.66	Husband smoked 20+ cigs/day	2.90

APPENDIX A

Excluded studies and additional references

A1. Introduction

As described in Section 2, a number of studies were not included in the database because they failed certain criteria for selection. Listed below in Section A2 are the excluded studies, together with the principal reasons for their rejection.

For some studies included in the database, interim results were reported in an early paper and then superseded by final results in a later paper. Section A3 lists those papers describing interim results which are generally not considered in the database.

The main reference to each study in the database is given in Section 16. With very few exceptions (described in Appendix B) that reference provides all the data needed for the report. For a number of the studies, additional reports have been published, which usually repeat some or all of the results cited in the main reference. For completeness Section A4 lists the additional papers relating to each study.

Finally all the actual additional references cited are given in Section A5.

A2. Studies excluded from the database

First author (year)	Reason for rejection
Knoth (1983)	Study has no control population.
Miller (1984)	Only 5 cases of lung cancer, results not separately presented.
Ziegler (1984)	Data only presented (by Dalager (1986)) in combination with those of Buffler and Correa studies. One can infer that there was some negative association in males with ETS exposure but no relative risk estimates can be obtained.
Sandler (1985)	Only 2 cases of lung cancer included.
Lloyd (1986)	Results not presented for never smokers.
Reynolds (1987)	Results only presented for cancers of smoking-related sites, not lung cancer.
Axelson (1988)	Study designed to investigate effects of radon, and the controls, containing many with smoking-related diseases, are not appropriate for ETS risk calculations. Also not

	stated if the ETS findings relate to never smokers or not.
Katada (1988)	Numbers of never smoking cases and controls that were unexposed to ETS too small to obtain any sort of reliable relative risk estimates.
Li (1989)	Results not presented for never smokers.
Ye (1990)	Results not presented for never smokers.
Sandler (1989)	Results only presented for cancers of smoking-related sites, not lung cancer.
Chen (1990)	Results seem not to be for never smokers and index of ETS exposure unstated.
Miller (1990)	Results concern respiratory, not lung cancer and only include 3 cases in spousal smoking analyses.
Holowaty (1991)	Results not presented for never smokers.
Ger (1993)	Results not presented for never smokers.
Lan (1993)	Index of ETS exposure not given, unstated if the results are for never smokers, and the odds ratios and confidence limits inconsistent with each other and with the tabular data given.
Siegel (1993)	Concerns lung cancer risk in food service workers, thought to have high ETS exposure - data generally for smokers and nonsmokers combined.
Miller (1994)	Control group, formed from decedents from all causes of death except lung cancer, so contains many with smoking related diseases.
Wang (1994) and Wang (1996)	Believed to be based on a subset of subjects from the Wu-Williams study.
Dai (1996)	Exposure to ETS recorded (source unstated) but not significant in regression analysis and relative risk not given.
Luo (1996)	Results not presented for never smokers.
Yu S-Z (1996)	Gives pooled odds ratio for ETS from 3 case-control studies in China. Two studies are Li (1989) and Ye (1990), already rejected, and the third is Xu (1989) which actually gives no data whatsoever on ETS.
Yu Z-F (1996)	Results not presented for never smokers.

A3. Papers describing interim results of studies in the database

Study Ref/author		Superseded paper: First author (year)
4	Trichopoulos	Trichopoulos (1981)
6	Hirayama	Hirayama (1981)
24	Hole	Gillis (1984)
36	Fontham	Fontham (1991)
40	Kabat 2	Kabat (1990)

A4. Further papers describing the studies considered in the database

Study Ref/author		Further paper: First author (year)
2	Chan	Chan (1979), Lam (1988)
6	Hirayama	Hirayama (1984b, 1985, 1987, 1988, 1990, 1990b)
9	Lam W	Lam (1988)
16	Koo	Koo (1983, 1984, 1985, 1988), Lam (1988)
17	Lam T	Lam (1988)
18	Pershagen	Pershagen (1988)
25	Svensson	Svensson (1988)
26	Janerich	Varela (1987)
28	Sobue	Sobue (1990b)
30	Liu Z	He (1991)
32	Brownson	Alavanja (1995)
35	Du	Du (1995, 1996), Lei (1996)
36	Fontham	Fontham (1993, 1993b)
41	de Waard	Ellard (1995)
42	Shen	Shen (1996b), Shen (1996c)

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APPENDIX B

Extraction of data from source material

In extracting the relative risks and 95% CIs from the source material for each study several general rules were kept to:

1) Where studies presented appropriate data on numbers of cases and controls for the exposure categories of interest, unadjusted relative risks and 95% CIs were calculated using the CIA program based on the methods described by Morris and Gardner [62]. These calculated values were used in the tables in these reports whether or not they agreed with the data given by the author.
2) Adjusted relative risks and 95% CIs were also calculated using the Mantel-Haenszel stratified procedures available in the CIA program where (which was rarely the case) the source paper presented the data in sufficient detail to allow this.
3) Where data on numbers of cases and controls were not presented, unadjusted or adjusted relative risks and CIs were taken as given in the paper, with 90% CIs converted to 95% CIs if necessary. On occasion, relative risks and CIs for overall exposure were estimated from values given by level of exposure.
4) Where, for a particular exposure, more than one set of adjusted relative risks and CIs relating to differing adjustment variables were presented, the values used in the tables were those based on the most extensive set of adjustment variables.

In most studies there were no problems in using these general rules to extract the data, and no more comment need be made. However, for the studies listed below, some clarification is needed on how the data were extracted:

Garfinkel 1 [1] Table 4 of ref 1 gives the numbers of observed and expected deaths according to husband's smoking. The populations at risk given in Appendix D, used to calculate the unadjusted relative risk and 95% CI, were obtained by splitting the total population of 176,739 given in the text of the paper according to the expected values. Note that because the expected deaths are age-adjusted, this produces age-adjusted relative risks. Calculating completely unadjusted relative risks based on the data presented in ref 1 would have given a value of 0.53 for spousal smoking, very different indeed both from the age-adjusted relative risks given in

Table 4 of ref 1 and the age and covariate-adjusted relative risks given in Table 5 of ref 1. As use of completely unadjusted data would have distorted the misclassification-adjusted analyses severely, it was decided to treat the age-adjusted data as the unadjusted data for the purposes of this review. Note that, in virtually all other studies (except Cardenas [37] - see below) age adjustment made little difference, so such procedures were not needed.

Correa [3] Results extracted for childhood exposure are for lifelong nonsmokers.

Hirayama [6] Virtually all results reported by Hirayama relating to husband's smoking are adjusted for the age of the husband, which is clearly inappropriate. Table 2 of ref 6 does give data by wife's age. These have been used in this review.

Garfinkel 2 [8] For the main spousal results the data relating to "husband's total smoking habits" rather than to "husband's smoking habits at home" have been used, the former being closer to those used in most of the other studies. Note that a large number of CIs calculated differ from those in ref 8. There seems to have been an error in the software used in this study.

Lam W [9] See Lam and Cheng (1988) for the data on spousal smoking.

Wu [10] The unadjusted data are given in Table 11 of the 1986 US Surgeon-General's Report.

Lee [12] Data on histological type do not appear in ref 12 but are given in Lee (1992).

Brownson 1 [13] Ref 13 only gives adjusted data. The unadjusted data appear in the EPA report [53] as a personal communication from Brownson.

Gao [14] The relative risk in Table 2 compares those who have lived with a smoking husband for 20+ and <20 years.

Koo [16] Note that the workplace data come from Koo (1984). Also that, for both the childhood and workplace data, the relative risks relate to that specific exposure, ignoring other exposures.

Butler [19] Butler's thesis concerns the results of two cohorts. The results relating to the AHSMOG cohort have not been used as they are not restricted to lifelong nonsmokers. The result cited are for the Spouse - Pairs cohort, based on Table 5.2 of ref 19 together with the text on p104. Table 5.3 is not used as it is also not restricted to nonsmokers.

Shimizu [22] Knowing that the study involves 90 never smoking cases and 163 never smoking controls, the 2x2 tables, and hence the RRs and 95% CIs can be calculated from the data in Table 1 of ref 22.

Hole [24] The numbers of exposed and unexposed cases and the at-risk population can be inferred from data presented in Tables I, V and VI of ref 24.

Svensson [25] The ETS data appear in Table 7 of ref 25, which involves a total of 34 never smoking cases and 174 never smoking controls. Table 3 of ref 25 gives 172 smoking cases and a relative risk for active smoking of 6.10. These data allow the whole of the data in Appendix D to be calculated.

Janerich [26] Table 3 of ref 26 gives relative risks in relation to spouse smoking of 0.93 for direct interviews and 0.44 for surrogate interviews. An average, weighted on the inverse of the variance, is 0.75. It is noted in the table footnote that there were 188 pairs with relevant data. The footnote to Table 1 of ref 26 gives 45 male and 146 female pairs out of 191. It has been assumed that 44 male and 144 female pairs had relevant data. Varela (1987) makes it clear that relative risk estimates vary little by sex. Given that about 60% of females and 40% of males are exposed (based on other US studies), the relevant data can then be estimated.

Brownson 2 [32] Results extracted are those presented for lifelong nonsmokers. Ref 32 does not give data for overall workplace exposure. The results given in Table 16 come from comments submitted by W J Butler on OSHA's proposed indoor air quality rules.

Stockwell [33] The 2x2 table in Appendix D was estimated from the relative risk and CI given of 1.6 (0.8-3.0), assuming that the ratio of the numbers of cases and controls with relevant data was approximately the same as the ratio for the overall sample, and assuming that about 60% of controls were exposed to their husband's smoking, a figure which was an average of control percentages for other US studies then available. The reason that the estimated numbers of cases and controls in the 2x2 table (62 and 91) is so much less than the total numbers of cases and controls in the study (210 and 301) is presumably because Stockwell used nonsmoking women with no household ETS exposure as the denominator omitting nonsmoking women with other exposures from the analysis.

Du [35] Results extracted are based on combining the data for the two types of control group presented in Tables 2 and 3 of ref 35.

Cardenas [37] For the same reason given for Garfinkel 1 [1] the "unadjusted" results given in the tables are actually age-adjusted. The populations at risk given in Appendix D are calculated by subdividing the total at-risk population so as to give the age-adjusted relative risks reported by Cardenas.

Zaridze [39] The data given in the original paper in Russian had some errors in it. A corrected table, provided by Zaridze as a personal communication to Prof N J Wald in 1996, contains the corrected data.

Kabat 2 [40] Note that Table 2 of ref 40 contained some errors and a corrected version appeared in Kabat (1996).

de Waard [41] The study provides no data on spousal smoking. Results for comparison of risk by cotinine level appear in Tables 22 and 23 (total exposure). Note that, while ref 41 does not state that ex-smokers were excluded from analysis, this becomes clear from an associated paper

on the same study (Ellard 1995).

Shen [42] The main text of ref 42 concerns a study in which nonsmokers have not been separated out. The only data for nonsmokers, which relate to a different study, are given in the last paragraph of p S110 of ref 42.

Sun [43] The 2x2 table in Appendix D was estimated from the relative risk and CI given and from knowledge of frequency of husband's smoking in other Chinese studies. The estimated relative risk and CI is almost identical to the adjusted relative risk and CI given in ref 43. Ref 43 does not provide unadjusted data.

Wang S-Y [44] Ref 44 mainly concerns analyses for smokers and nonsmokers combined. The only results for never smokers are given on p S104. On this page it states that there are 99 female cases of which 83% are never smokers, i.e. 82. It also states that the active smoking relative risk is 4.0 and that there are 98 female controls. Assuming 94 are never smokers gives a relative risk closest to 4. The 2x2 table in Appendix D is consistent with the relative risk and CI given by Wang; but implies a frequency of exposure of 82% in cases, conflicting slightly with the statement that 87% of cases were exposed to ETS at home and that 63% were exposed in the workplace.

Schwartz [46] Unadjusted and adjusted relative risks for ETS exposure at home and at work can be obtained for sexes combined from the data in Table 2 of ref 46. Elsewhere it is stated that 72% of cases and 64% of controls are females, i.e. 67.85% of the sample of 257 cases and 277 controls are female and 32.15% are male. It was assumed sex-specific relative risks were the same as for the sexes combined, but that the inverse-variance weights were reduced by factors of 0.6785 (female) and 0.3215 (male).

References

References in square brackets are those cited in the main text of this review. Other references are given in Appendix A.

APPENDIX C

Risk factors taken account of in relative risk estimation

Table C1 summarizes, for each of the 46 studies, the extent to which potential confounding factors have been taken into account in relative risk estimation.

1. Age Thirty-three studies are marked as "yes" in Table C1. Most of these adjusted for age in analysis, while some (see below) used age-matched lifelong nonsmoking cases and controls. Many of the studies marked as "no" age-matched overall cases and controls or noted that the age-distribution of the overall cases and controls was similar. However this provides no guarantee that the age distribution of the selected lifelong nonsmoking cases and controls is similar.

2. Marital status It was clear that for 14 of the studies, marked as "yes" in Table C1, attention was specifically restricted to married women, when comparing risk according to whether or not their husband smoked. The remaining 22 studies which reported risk in relation to husband's smoking (the 10 that used other indices are marked "NA" = not applicable) appeared to include some unmarried women in their analyses. Failure to exclude unmarried women in analyses using husband's smoking as an index, leads to a clear confounding of possible effects of ETS and marital status, since all the exposed women will be married, but some of the unexposed women will not.

3. Other risk factors Seventeen of the 46 studies, marked as "none" in Table C1 appeared to take no other potential confounding variables at all into account in the relative risk estimation for ETS and, for one study (Shen), it was not clear whether reported relative risks were adjusted or not. For some studies, comments additional to those given in the tables should be made:

   Janerich Lifelong nonsmoking cases and controls were individually matched on age and residence, the statistical analyses adjusting for the matching factors.

Du, Kabat 1, Lifelong nonsmoking cases and controls were individually matched on age and the matching factors noted, but no adjustment was made in analysis.

Kabat 2 Lifelong nonsmoking cases and controls were individually matched on age, race, hospital and date of interview. Some analyses in the tables adjust for age, type of hospital and years of education.

Garfinkel 2 and Shimizu Lifelong nonsmoking cases and controls were individually matched on age and hospital. The other risk factors cited were only used in regression analyses, the results from which could not be incorporated into the tables.

Hirayama In his analyses relating to husband's smoking Hirayama only presented one set of results adjusted for the **wife's** age and these, which have been used in this review, took into account no other potential confounding factors. Results from analyses adjusting for **husband's** age and other risk factors such as husband's occupation and drinking habits, are not included in the Tables.

Hole Social class was only taken into account in the combined sex analyses relating to spousal smoking. These are not included in the Tables.

Wang T-J ETS exposure and other risk factors were considered in a multiple regression analysis. As ETS was not significant, no adjusted relative risks were presented.

Lee and Stockwell Additional risk factors were considered as potential confounders but were not adjusted for in the analyses presented as they were stated to have little effect. (It should also be noted that some other studies which took specific risk factors into account, such as Fontham, only adjusted in analysis for those factors that were considered most likely to have any potential confounding factors. A number of the studies considered would actually have recorded data on quite a large number of risk factors.)

The other risk factors most commonly mentioned in Table C1 were education/schooling (11 studies), race/ethnicity (9 studies), area of residence (7 studies), occupation (6 studies), medical status (4 studies), hospital (4 studies), income/SES (3 studies) and diet (3 studies).

TABLE C1

Risk factors taken account of in relative risk estimation

Study Ref	Author	Location	Age	Marital status	Other risk factors
1	Garfinkel 1	USA	Yes	Yes	Occupation, education, race, urban or rural residence, absence of serious disease
2	Chan	Hong Kong	No	NA	None
3	Correa	USA	No	Yes	None
4	Trichopoulos	Greece	No	No	None
5	Buffler	USA	No	NA	None
6	Hirayama	Japan	Yes	Yes	None
7	Kabat 1	USA	Yes	Yes	Race, hospital (matching factors)
8	Garfinkel 2	USA	Yes	No	Hospital (matching factors), socioeconomic status, year of diagnosis
9	Lam W	Hong Kong	No	Yes	None
10	Wu	USA	Yes	Yes	None
11	Akiba	Japan	Yes	Yes	City, vital status, participation in medical examinations
12	Lee	UK	Yes	Yes	Marriage ongoing or ended
13	Brownson 1	USA	Yes	NA	Income, occupation
14	Gao	China	No	Yes	None
15	Humble	USA	Yes	No	Ethnicity
16	Koo	Hong Kong	Yes	Yes	Live births, years since exposure ceased, schooling
17	Lam T	Hong Kong	No	No	None
18	Pershagen	Sweden	Yes	No	Vital status
19	Butler	USA	Yes	Yes	None
20	Geng	China	No	No	None
21	Inoue	Japan	Yes	Yes	District
22	Shimizu	Japan	Yes	No	Hospital (matching factor), occupational exposure to iron or other metals
23	Choi	Korea	No	No	None
24	Hole	Scotland	Yes	NA	Social class
25	Svensson	Sweden	Yes	NA	None
26	Janerich	USA	Yes	No	Residence (matching factor)
27	Kalandidi	Greece	Yes	No	Years of schooling, interviewer, total energy intake, fruit consumption
28	Sobue	Japan	Yes	No	Education, use of wood or straw
29	Wu-Williams	China	Yes	No	Education, study area
30	Liu Z	China	Yes	NA	Age of starting to cook, years of cooking
31	Joeckel	Germany	No	No	None
32	Brownson 2	USA	Yes	No	Previous lung disease
33	Stockwell	USA	Yes	No	Race, education
34	Liu Q	China	No	No	Education, occupation, living area
35	Du	China	Yes	No	Residence (matching factor)
36	Fontham	USA	Yes	No	Race, area, education, fruits, vegetables and supplemental vitamin index, family history of lung cancer, employment in high risk occupations
37	Cardenas	USA	Yes	Yes	Race, education, foods containing carotenoids, fat, occupational exposure to asbestos, history of chronic lung disease
38	Layard	USA	Yes	No	Race
39	Zaridze	Russia Yes	No	Air pollution	
40	Kabat 2	USA	Yes	Yes	Race, hospital, date of interview (matching factors), years of education
41	deWaard	Holland	Yes	NA	None
42	Shen	China	NK	NA	Not known (NK) if relative risk given was adjusted or not
43	Sun	China	Yes	No	Education
44	Wang S-Y	China	No	NA	None
45	Wang T-J	China	Yes	No	None
46	Schwartz	USA	Yes	NA	Race

C4

APPENDIX D

Data used in misclassification adjusted analyses of lung cancer risk associated with husband's smoking

For data relating lung cancer to smoking by the husband, results of analysis adjusted for smoking habit misclassification by the method of Lee and Forey [63] are presented in Tables 8 and 9. The data used in these analyses are given in Table D1. In order to conduct misclassification-adjusted analyses one needs to have, for each study, the numbers of ETS exposed and unexposed cases and controls who have never smoked (columns 1 to 4 of Table D1) together with either the total numbers of cases and controls who have ever smoked (columns 5 and 6), or an estimate of the percentage of controls who have ever smoked (column 7) and an estimate of the relative risk for ever/never smoking (column 8). The data in columns 1 to 4 of Table D1 are consistent with the unadjusted relative risks and 95% CIs given in Table 2. Data are only given in columns 5 and 6 if they can be obtained directly (or, in the case of study 31, indirectly) from the source reference. For some studies, which only provided data relating to never smokers, the data in columns 7 and 8 had to be estimated. In these studies, the estimates, shown in brackets, are either taken from the EPA report [53] or, in the case of more recent studies, estimated using comparable methods.

D2

TABLE D1

Data used in misclassification adjusted analyses of lung cancer risk associated with husband's smoking

Study Ref	Author	Never smoked Cases Exposed (1)	Never smoked Cases Unexposed (2)	Never smoked Controls* Exposed (3)	Never smoked Controls* Unexposed (4)	Ever smoked Cases Total (5)	Ever smoked Controls Total (6)	% Controls Ever Smoked (7)	Relative Risk Ever/Never (8)	Notes
1	Garfinkel 1	88	65	94880	81859	-	-	(22.0)	(3.58)	e
2	Chan	34	50	66	73	105	50	26.5	3.48	d
3	Correa	14	8	61	72	244	119	47.2	12.40	d
4	Trichopoulos	53	24	116	109	25	26	10.4	2.81	d
5	Buffler	33	8	164	32	412	279	58.7	7.06	d
6	Hirayama	163	37	69645	21895	121	17366	15.9	3.19	d
7	Kabat 1	13	11	15	10	-	-	(42.0)	(5.90)	e
8	Garfinkel 2	91	43	254	148	-	-	(34.0)	(6.00)	e
9	Lam W	37	23	64	80	70	41	22.2	4.10	d
10	Wu	19	9	33	22	120	87	61.3	2.71	d
11	Akiba	73	21	188	82	58	70	20.6	2.38	d
12	Lee	22	10	45	21	226	101	60.5	4.62	d
13	Brownson 1	4	15	7	40	33	19	28.8	4.30	d
14	Gao	189	57	276	99	236	130	25.7	2.77	d
15	Humble	15	5	91	71	223	111	40.7	16.27	d
16	Koo	51	35	66	70	112	63	31.7	2.81	d
17	Lam T	115	84	152	183	242	106	24.0	3.84	d
18	Pershagen	37	33	153	141	-	-	(37.0)	(4.20)	e
19	Butler	3	5	10579	43052	-	-	(14.0)	(4.00)	e
20	Geng	34	20	41	52	103	64	40.8	2.77	d
21	Inoue	18	4	30	17	7	7	13.0	2.14	d
22	Shimizu	52	38	91	72	-	-	(21.0)	(2.80)	e
23	Choi	49	26	88	76	20	26	13.7	1.68	d
24	Hole	5	1	1295	489	25	2253	55.8	3.30	d
25	Svensson	24	10	114	60	172	144	45.3	6.11	d
26	Janerich	76	68	86	58	-	-	(42.0)	(8.00)	e
27	Kalandidi	64	26	70	46	63	25	17.7	3.25	d
28	Sobue	80	64	395	336	-	-	(21.0)	(2.81)	e
29	Wu-Williams	205	212	331	271	539	351	36.8	2.22	d
30	Liu Z	45	9	176	26	-	-	(32.1)	(3.01)	c
31	Jockel	17	6	25	20	(56)	(47)	51.0	2.35	g
32	Brownson 2	218	213	598	568	-	-	(43.0)	(8.00)	f
33	Stockwell	44	18	55	36	-	-	(42.0)	(8.00)	f
34	Liu Q	25	13	37	32	54	23	25.0	4.26	d
35	Du	47	28	154	100	-	-	(32.1)	(3.01)	c
36	Fontham	433	218	766	487	-	-	(43.0)	(8.00)	e
37	Cardenas	113	51	142439	70715	-	-	(42.4)	(7.81)	d
38	Layard	15	24	961	969	-	-	(34.0)	(6.00)	f
39	Zaridze	92	70	126	159	-	-	(15.0)	(4.00)	r
40	Kabat 2	41	26	102	71	-	-	(42.0)	(8.00)	f
43	Sun	(144)	(86)	(136)	(94)	-	-	(32.1)	(3.01)	cs
44	Wang S-Y	(67)	(15)	(60)	(34)	-	-	5.1	4.0	t
45	Wang T-J	92	43	89	46	-	-	(32.1)	(3.01)	c
46	Schwartz	(124)	(61)	(112)	(65)	-	-	(42.0)	(8.00)	u

Footnotes

* Or populations at risk for prospective studies

c Bracketed data in columns 7 and 8 estimated from average for other Chinese studies [14, 20, 28, 33] with data available.

d Complete data in table available or can be calculated directly from source.

e Bracketed data are estimates as given in the EPA report [53].

f Bracketed data are estimates comparable to those given in the EPA report [53] for other US studies conducted at the same time; studies themselves not considered by EPA.

g Data given in form which does not allow exact numbers of ever smoking cases and controls to be calculated; bracketed data are best estimates.

r Bracketed data are approximate estimates based on very limited data.

s Numbers of never smoking cases and controls not given in the source reference and have been estimated from relative risk and confidence interval given and from knowledge of frequency of husband's smoking in other Chinese studies.

t Number of never smoking cases and controls not given in the source reference and have been estimated from data given on relative risk, confidence interval and approximate frequency of exposure.

u Numbers of never smoking cases and controls estimated from data for sexes combined, assuming association of lung cancer with ETS and frequency of exposure same in females; frequency of smoking and smoking relative risk based on other US studies conducted at the same time.

APPENDIX E
Some study characteristics

Table E1 lists various characteristics of the studies included in the database. The key to Table E1 is given below.

Table E2 gives the main reason why 18 of the 46 studies have been considered to be of poor quality, based on the criteria of Lee [69].

Key to Table E1

Study: A 4 character abbreviation of the study first author.

Ref: The study reference as in the main document

Year of publication: Last 2 digits of year are given.

Location: C = China G = Greece HK = Hong Kong J = Japan K = Korea R = Russia US = United States WE = Western Europe.

Considered by ISCSH: + = Considered by Independent Scientific Committee on Smoking and Health, in some cases based on an earlier publication.

Study type: P = Prospective C = Case-Control NC = Nested Case-Control.

Nonsmoking cases: Numbers of nonsmoking cases are shown separately for females (F) and for males (M). The numbers shown are the total numbers, if available, or, if not, the numbers in the spousal smoking analyses. Some analyses of specific ETS endpoints are based on smaller. numbers of cases than shown here, due to exclusion of ineligibles.

100% histological confirmation: + = 100% histological confirmation.

Data available by histological type: + = The publication contains ETS/lung cancer relative risks by histological type.

Type of control group: P = Prospective study (no controls) H = Healthy D = Diseased B = Both healthy and diseased U = Unstated

% proxy responses: For those studies using proxy responses the percentage of proxy responses is given for cases and for controls separately. For some studies these percentages refer to all cases and controls and not to the nonsmoking cases and controls analysed. NK = not known.

Study quality poor: + = Those studies defined as of poor quality using the criteria of Lee [69]. The actual reasons why the studies are defined as such are given in Table E2.

Dose-response data available: + = The study presented data on risk by extent, by duration, or by extent times duration, of ETS exposure.

Index of spousal exposure (used in Table 2): E = Spouse ever smoked, M = Spouse ever smoked in marriage, C = Spouse current smoker, H = Exposed at home, HW = Exposed at home or work. Study 41 only recorded exposure by cotinine level and study 42 only reported results for exposure to 20+ cigs/day (from unstated source) so their results are not included in Table 2.

Index of childhood exposure (used in Table 18): M = Mother F = Father P = Parents H = At home A = Any. Studies with no entry did not report results for childhood exposure.

Workplace exposure studied: + = Workplace exposure studied

Social exposure studied: + = Social exposure studied

TABLE E1

Study characteristics

Characteristic	Study Ref	GAR1 1	CHAN 2	CORR 3	TRIC 4	BUFF 5	HIRA 6	KAB1 7	GAR2 8	LAMW 9	WU 10	AKIB 11	LEE 12
Year of publication		81	82	83	83	84	84	84	85	85	85	86	86
Location		US	HK	US	G	US	J	US	US	HK	US	J	WE
Considered by ISCSH		+	+	+	+		+	+	+				+
Study type		P	C	C	C	C	P	C	C	C	C	NC	C
Nonsmoking cases	F	153	84	25	77	41	200	53	134	75	31	94	32
	M			10		11	64	25				19	15
100% histological confirmation						+		+	+		+		
Data available by hist type					+				+	+	+		+
Type of control group		P	D	D	D	B	P	D	D	D	H	D	D
% proxy responses - cases/				24		84			88			90	
controls				11		81			NK			88	
Study quality poor				+	+				+	+			
Dose-response data available		+		+	+	+	+		+		+	+	
Index of spousal exposure		C	HW	E	E	H	E	E	E	E	M	E	M
Index of childhood exposure				M					A		P	P	
Workplace exposure studied								+	+		+		+
Social exposure studied									+				+

Characteristic	Study Ref	BRO1 13	GAO 14	HUMB 15	KOO 16	LAMT 17	PERS 18	BUTL 19	GENG 20	INOU 21	SHIM 22	CHOI 23	HOLE 24
Year of publication		87	87	87	87	87	87	88	88	88	88	89	89
Location		US	C	US	HK	HK	WE	US	C	J	J	K	WE
Considered by ISCSH					+	+	+						+
Study type		C	C	C	C	C	NC	P	C	C	C	C	P
Nonsmoking cases	F	19	246	20	88	202	83	8	54	28	90	75	6
	M			8								13	3
100% histological confirmation		+		+		+		+			+	+	
Data available by hist type		+			+	+	+						
Type of control group		D	H	H	H	H	H	P	U	D	D	D	P
% proxy responses - cases/		69		52						100			
controls		39		0						100			
Study quality poor		+		+		+		+	+	+			+
Dose-response data available			+	+	+	+	+		+	+		+	+
Index of spousal exposure		HW	M	E	M	M	M	M	E	E	M	M	H
Index of childhood exposure			H		H		P						
Workplace exposure studied					+						+		
Social exposure studied													

TABLE E1 (Continued)

Study characteristics

Characteristic	Study Ref	SVEN 25	JANE 26	KALA 27	SOBU 28	WUWI 29	LIUZ 30	JOCK 31	BRO2 32	STOC 33	LIUQ 34	DU 35	FONT 36
Year of publication		89	90	90	90	90	91	91	92	92	93	93	94
Location		WE	US	G	J	C	C	WE	US	US	C	C	US
Considered by ISCSH													
Study type		C	C	C	C	C	C	C	C	C	C	C	C
Nonsmoking cases	F	38	146	91	144	417	54	23	432	210	38	75	653
	M		45					10					
100% histological confirmation			+		+					+			+
Data available by hist type			+	+					+	+			+
Type of control group		B	H	D	D	H	H	H	H	H	D	D	H
% proxy responses - cases/			33						65	67		100	37
	controls		33						0	0		100	0
Study quality poor		+	+	+					+	+		+	+
Dose-response data available			+	+					+	+	+	+	+
Index of spousal exposure		HW	M	M	M	M	H	M	M	M	C	C	M
Index of childhood exposure		M	H		M	M			H	H			H
Workplace exposure studied			+	+		+			+	+			+
Social exposure studied			+							+			+

Characteristic	Study Ref	CARD 37	LAYA 38	ZARI 39	KAB2 40	DEWA 41	SHEN 42	SUN 43	WNGS 44	WNGT 45	SCHW 46
Year of publication		94	94	94	95	95	96	96	96	96	96
Location		US	US	R	US	WE	C	C	C	C	US
Considered by ISCSH											
Study type		P	C	C	C	NC	C	C	C	C	C
Nonsmoking cases	F	246	39	162	69	23	70	230	82	135	185
	M	116	21		41						72
100% histological confirmation				+	+		+	+	+		+
Data available by hist type							+	+			
Type of control group		P	D	D	D	H	U	H	D	H	H
% proxy responses - cases/			100								83
	controls		100								22
Study quality poor			+				+			+	+
Dose-response data available		+	+		+	+				+	
Index of spousal exposure		E	E	C	E			M	HW	M	H
Index of childhood exposure				F	H			A		A	
Workplace exposure studied				+	+			+		+	+
Social exposure studied					+						

TABLE E2

Reasons for defining certain studies as of poor quality

Study Ref/author		Main reason for defining study as of poor quality
3	Correa	More next-of-kin respondents in cases than controls
4	Trichopoulos	Cases and controls from different hospitals
8	Garfinkel 2	More next-of-kin respondents in cases than controls
9	Lam W	Cases and controls from different hospitals
13	Brownson 1	More next-of-kin respondents in cases than controls
15	Humble	Only cases have next-of-kin respondents
17	Lam T	Cases interviewed in hospital, controls elsewhere
19	Butler	Less than 10 cases
20	Geng	Control group undescribed
21	Inoue	All respondents next-of-kin
24	Hole	Less than 10 cases
25	Svensson	Cases interviewed in hospital, controls elsewhere
26	Janerich	Cases and controls unmatched on vital status *
27	Kalandidi	Cases and controls from different hospitals
32	Brownson 2	Only cases have next-of-kin respondents
33	Stockwell	Only cases have next-of-kin respondents
35	Du	All respondents next-of-kin
36	Fontham	Only cases have next-of-kin respondents
38	Layard	All respondents next-of-kin
42	Shen	Control group undescribed
45	Wang T-J	Cases interviewed in hospital, controls elsewhere
46	Schwartz	More next-of-kin respondents in cases than controls

* Also applies to studies 13, 15, 32, 33, 46.

APPENDIX F

Strengths and weaknesses of the major studies

F1. Introduction

In this Appendix a brief description is given of each of the studies involving over 100 lung cancer cases, commenting particularly on their main strengths and weaknesses. The studies are considered in chronological order of publication.

F2. Garfinkel 1 [1]

In this prospective study, Cancer Prevention Study I (CPS-I), somewhat over a million men and women were enrolled by volunteer workers of the American Cancer Society in 1959 and 1960. All members of the households involved aged over 30 completed a detailed questionnaire on a range of risk factors, with briefer repeat questionnaires completed in 1961, 1963, 1965 and 1972. Mortality status was determined at regular intervals and death certificates obtained. The study population is not fully representative of the USA, being mainly white and of higher social status and less exposed to occupational risk factors than average. Garfinkel did not collect ETS exposure data specifically, relying on data on smoking status for married subjects who were both in the study. The strengths of the study include its prospective design, its great size, the completeness of follow-up, and the large number of risk factors recorded.

F3. Hirayama [6]

In this prospective study somewhat over a quarter of a million adults aged 40+ and resident in six prefectures in Japan were interviewed at home during 1965 by trained public health nurses and midwives using a simple one page questionnaire. The population was followed up from census records and death certificates, but no further interviews were conducted, except on a small sample in 1971. Questions on ETS exposure were not asked, reliance being placed on data on smoking status collected for married subjects who were both in the study. Despite its prospective design and large size, the study has a number of deficiencies including: (i) Data on smoking habits were collected only once during a 16-year follow up period; (ii) Subjects migrating out of the prefectures were not followed up for mortality; (iii) Only limited data on confounding variables were collected; (iv) Reliance was placed on death certificate diagnosis; (v)

Hirayama, with one exception, always presented results for nonsmoking women adjusted for the age of the husband and not, as is appropriate, the age of the wife; (vi) Hirayama is known to have made a number of simple errors in statistical analysis; and (vii) Death rates in the study were much lower than expected, apparently because mortality tracing was incomplete, with deficits varying by demographic factors.

F4. Garfinkel 2 [8]

The paper describes results from a case-control study carried out in one Ohio and three New Jersey hospitals. The main analyses compared ETS exposure among 134 nonsmoking female lung cancer cases and 402 nonsmoking female colorectal cancer controls. The cases and controls were drawn from a larger number of cases and controls diagnosed in 1971-1981. Subjects with no reported smoking history in their hospital records were originally selected. Repeat interviews were then carried out with the subject, if still alive, or with the next of kin or other informant who had known the subject for at least 25 years. Subjects found to have smoked were excluded, as were those found not to have lung cancer on review of the histology, the objective being to include only definite never smokers with confirmed cancer. Of 283 women originally selected as lung cancer cases with no original evidence of smoking, 113 (40%) were found to be smokers on re-interview, while 36 (13%) were proven not to have lung cancer. Controls were matched 3:1 for age, hospital and interviewer, the interviewer being blind both to the diagnosis and the study objective. A wide range of different indices of ETS exposure was used and analyses were standardized or matched for some or all of age, hospital, socio-economic status, and year of diagnosis. The study has a number of obvious strengths, including careful confirmation of diagnosis and of never smoking status, the blindness of the interviewer, and the extensiveness of the analyses presented. Limitations of the study include collection of relatively few data on potential confounding variables and use of a substantially higher proportion of next-of-kin respondents in cases than in controls. Also, some of the confidence intervals presented in the paper seem to be erroneous, being inconsistent with the tabulated data presented, and in some analyses where tabulated data were not given, being impossibly narrow given the numbers of cases and controls studied.

F5. Akiba [11]

From a cohort of 110,000 Hiroshima and Nagasaki atomic bomb survivors

followed since 1951, 525 cases of primary lung cancer diagnosed during 1971-80 were identified, as were 1167 controls matched on sex, year of birth, city of residence, vital status, and whether they were participating in a programme of biennial medical examinations. Interviews were sought during 1982 with all cases and controls or their next of kin who lived in the three cities, with questionnaires completed by 428 cases and 957 controls. Information was obtained on cigarette smoking history, smoking by the spouse, and also demographic, medical, occupational and other factors. Limitations of the study include: (i) information was only obtained for about 80% of cases and controls, (ii) the controls included a substantial number of patients who had died from smoking-related diseases, including 13% from coronary heart disease and 26% from stroke, (iii) almost half the lung cancer diagnoses were based only on cytology, radiology or clinical findings, and (iv) information was obtained from the subjects themselves for only 10% of cases and 12% of controls, with over half the information being obtained from someone other than the subjects or their spouses.

F6. Gao [14]

In this case-control study, 765 female lung cancer cases aged 35-69 were identified to have occurred between urban Shanghai in 1984-86. Interviews were conducted with the 672 who were still alive and with 735 population-based controls who were selected to have a similar age distribution to the cases. Data were collected on ETS exposure in childhood, from the husband, and generally in adult life, and on a range of other risk factors. Only 43% of the cases were diagnosed by tissue biopsy. The results relating to ETS are not clearly presented. Thus it is not made totally clear whether results relating to childhood or adult life exposure are restricted to never smokers or not. Furthermore, the only table relating risk in never smoking women to living with a smoking husband gives risk related to <20, 20-29, 30-39 and 40+ years exposure without making it clear if the first group includes women married to nonsmoking husbands. No results are presented comparing never smokers whose husbands did or did not smoke.

F7. Lam T [17]

In this case-control study, conducted in 1983-85, 445 Chinese women in Hong Kong with histologically or cytologically confirmed lung cancer and 445 individually age, race and residence matched neighbourhood controls were asked about their own smoking habits, those of their spouse, and other variables. One important possible source of bias in this study results from the lack of comparability of circumstances of interview of the cases and controls. Cases were interviewed in hospital, following diagnosis. For controls, 'the interviewer went to the address of the case and started to visit the nearest neighbourhood addresses until she found a woman who appeared healthy and was within 5 years of the age of the case' [17]. Apparently many of the controls were interviewed in the street [54].

F8. Janerich [26]

In this case-control study, 439 lung cancer cases aged 20-80 who were resident in upstate New York had a histologically confirmed diagnosis of lung cancer and who were either never smokers or long-term ex smokers were interviewed, as were 439 population controls (registered car drivers) individually matched to the cases on age, sex, country of residence, and never/ex smoking status. Interviews were conducted with the respondent in 67% of the case control pairs and with a surrogate in 33%, with data being collected on six indices of ETS exposure, on smoking by the subject, and on various potential confounding variables. Results were separated for never and ex-smokers. While the study has various strengths, including its quite large size, its insistence on histological confirmation, its matching on self/surrogate interviewer, and the fact that it carried out a number of independent studies to try to confirm smoking status, a limitation of the study design is that it compared, partly, interviews conducted with surrogates of **dead** cases and **living** controls. However relative risks were stated to vary little by source of information. The study in general found little evidence of an association of ETS with lung cancer risk. A weakness of the paper was that it highlighted a single association noted with person-years of exposure to household smoking, without noting the statistical problem of multiple testing or adjusting for number of persons in the household, with which the index is clearly correlated.

F9. Sobue [28]

This case-control study, carried out in eight hospitals in Osaka, Japan between 1986 and 1988, involved a total of 144 female lifelong nonsmoking histologically confirmed lung cancer cases and 731 unmatched female lifelong nonsmoking controls with diagnoses other than lung cancer (mainly neoplastic diseases). The patients, who were aged 40-79 at the time of admission, completed a questionnaires in hospital concerning smoking, ETS and indoor air pollution. One limitation of the study is that, although the study was conducted in multiple hospitals, this seems not to have been taken into account in design or analysis, so that the distribution of hospitals might have varied between cases and controls. Also the controls had a mixture of diseases, some associated with smoking. Sobue noted that the results were unaffected by exclusion of breast cancer patients from the control group, but did not provide any more information as to whether the results might have depended on the specific controls used. Sobue collected data on histological type of lung cancer, but only presented results for all types combined.

F10. Wu-Williams [29]

The paper describes combined results for women from two large case-control studies conducted in Harbin and Shenyang, China in 1985-87. A total of 965 women with newly diagnosed lung cancers and 959 randomly selected population controls were interviewed concerning ETS exposure, active smoking and a wide range of potential confounding factors. The strengths of the study include the large number of never smoking cases, the representativeness of both the cases and controls and the large number of lung cancer risk factors taken into account. The main weaknesses appear to relate, not to the study, but to the paper, which failed even to mention the statistically significant negative relationship seen with spousal smoking, failed properly to present results from the multivariate analyses conducted and also failed to take marital status and working status into account in the analyses, of respectively, spousal and workplace ETS exposure.

F11. Brownson 2 [32]

This case-control study, conducted in Missouri over the period 1986-1991, involved 618 lung cancer cases and 1402 population controls selected from driver's license and Medicare files, matched by age (30 to 84) and smoking status. Cases and controls consisted only of female lifelong nonsmokers and long-term exsmokers, results

being presented separately for lifelong nonsmokers. Data were collected on ETS exposure in considerable detail and on a range of potential confounding variables. Although the study involved more lifelong nonsmokers than any study previously conducted and collected extensive data, it has some weaknesses. Notably, data were collected from surrogates for 65% of the cases, while data for controls came wholly from the subjects themselves. Also histological confirmation was only available for 76% of cases, unlike the 100% typical of most US studies. The representativeness of the controls is also doubtful, partly because all women do not have a driver's licence or are Medicare members, and partly because of differential non-response rates. The paper is limited by failing to give enough details of its results, e.g. none for workplace exposure, and overemphasis of a single elevated risk estimate (associated with high levels of ETS exposure in adulthood) when the overall results were completely consistent with a lack of effect of ETS exposure.

F12. Stockwell [33]

This case-control study of nonsmoking women in Missouri involved 210 histologically confirmed cases diagnosed between 1987 and 1991 and 301 community-based controls of similar age and race identified through random-digit dialling. Data were collected on ETS exposure at home, at work and in social settings, but no details are given of what other information was recorded, although this must have included race, age, marital status and years of education. A weakness of the study was that surrogate respondents were used for a high proportion of cases, 67%, but for none of the controls. It is also unclear how representative the controls are, no information being given on their non-response rate. Apparent failure to collect, and certainly to adjust for, relevant potential confounding factors is also a problem. Data on smoking habits were collected from various sources, but no details were given on discrepancy rates or any attempt made to adjust for smoking habit misclassification. Nor was any attempt made to adjust for place of interview in the analysis, cases and controls being noted to differ. It should also be noted that all the relative risks presented in this study are relative to women unexposed to ETS from any source, not just from the source being analysed. This introduces an element of non-comparability in the findings from those in other studies.

F13. Fontham [36]

This is the largest case-control study ever carried out. Conducted in five

metropolitan areas in the US, it involved 653 lifelong nonsmoking cases with histologically confirmed lung cancer diagnosed in 1986-1990, 1253 controls selected by random digit dialling and random sampling from the Health Care Financing Administration files for women aged 65 years and older, and 351 controls with colon cancer. It has a number of obvious strengths:

(i) Extensive data were collected on ETS exposure and on a wide range of potential confounding variables which were adjusted for in analysis.

(ii) Insistence on histopathological confirmation of diagnosis, with an independent review of the slides by a pathologist specializing in pulmonary pathology;

(iii) Inclusion of healthy and diseased controls. Actually the 1994 paper [35] reports only the results for the healthy controls, it being demonstrated in an interim report (Fontham, 1991) that results were similar using either type of control;

(iv) Multiple sources of information were used to try to rule out the possibility that the patient might have been an ex-smoker;

(vi) The paper is well written and presents results in far more detail than the great majority of other studies in ETS and lung cancer.

However, despite these apparently impressive credentials, which have led to it being widely cited as a major reference, there are a number of weaknesses with the study. These include the following:

(i) The study is not, as has been claimed, representative of the US, with over 81% of cases and 86% of the healthy controls coming from California.

(ii) The proportion of adenocarcinomas was much higher than reported in other US studies, perhaps reflecting the diagnostic preferences of the reviewing pathologist.

(iii) It is unclear whether use of random digit dialling and random sampling from the Health Care Financing Administration files produces a representative sample. No attempt was made to ensure that cases in the study had telephones or were on the files.

(iv) The proportion of next-of-kin respondents was very different for the cases (37%), the colon cancer controls (10%) and the healthy controls (0%). The authors note, however, that results were similar for self and surrogate respondents.

(v) The attempt to exclude ex-smokers may lead to bias because the same sources of information are not available for cases and healthy controls. The latter will have

no hospital or physician records to check.

(vi) The use of urinary cotinine to exclude current smokers may not in fact reduce bias due to misclassification of active smoking. Eliminating true current smokers from cases reduces the relative risk estimate but eliminating true current smokers from controls increase it, and procedures that are much more successful in eliminating true current smokers from controls than from cases may actually **increase** misclassification bias. This was likely to be so here. In the first place, urine samples could not be taken from dead cases. Secondly, cotinine would not detect the quite high proportion of cases who would have been current smokers around the time of diagnosis but had given up subsequently.

(vii) The analyses presented in the paper did not restrict attention to married women when considering spousal exposure, or to working women when considering workplace exposure.

(viii) The authors misanalyzed the data concerning the joint association of lung cancer with adulthood and childhood exposure (see Part 12 and Table 24).

F14. Cardenas [37]

This was the second Cancer Prevention Study (CPS-II) conducted by the American Cancer Society, involving 1.2 million men and women aged 30 years or older enrolled using the same enrolment plan and organizational structure as CPS-I (see Garfinkel 2, section F2). Although conducted in all 50 US states, subjects were predominantly white and more educated than the general population. Interviewing was conducted in 1982, with mortality followed until the end of 1989. The questionnaire collected detailed data on a range of risk factors. As well as providing data on spousal smoking, the study, unlike CPS-I, also collected data on self-reported ETS exposure at home, at work and in other places. As with CPS-I, the strengths of the study include its prospective design, its great size, the completeness of follow-up and the large number of risk factors recorded. The study includes more male lung cancer cases with data on smoking by the wife than any other study (see Table 10).

F15. Zaridze [39]

This case-control study of nonsmoking women in Moscow conducted in 1991-1993 concerned 162 cases with a histologically confirmed lung cancer and 285 controls hospitalised at the same time with cancers other than of the upper respiratory tract. The

interview mainly concerned ETS exposure, residential and employment history, with at-home radon measurements made for a subset of patients. One limitation of the study is the likely inclusion of some patients with smoking related cancers in the control group. It should also be noted that there were obvious errors in the ETS data presented in the original paper, subsequently corrected in a letter to Prof N.J. Wald.

F16. Kabat 2 [40]

This case-control study involved 41 male and 69 female lifetime nonsmoking histologically confirmed lung cancer cases identified in six hospitals in four US cities (New York, Chicago, Detroit and Philadelphia). For each case enrolled, up to three control patients, admitted with diagnoses thought not to be associated with tobacco use, were selected, matched on age, sex, race, hospital and date of interview. All subjects were interviewed in person in hospital by trained interviewers who administered a questionnaire concerning demographics, alcohol intake, occupation, height and weight and a very detailed history of ETS exposure. Strengths of the study include conduct of the interview at the time of initial diagnosis, insistence on histological confirmation, avoidance of proxy respondents and the detail of the questionnaire on ETS. It should be noted that some relative risks published in the original paper were incorrect and subsequently corrected in an erratum.

F17. Sun [43]

This case-control study conducted in Harbin in China involves 230 lifelong nonsmoking female cases and an equal number of nonsmoking female population controls. The results are only reported in an abstract, which presents age and education adjusted relative risks and 95% CIs for a variety of indices of ETS exposure. There is no mention of when the study was conducted, what data on potential confounding variables were collected, or where interviews were conducted, though it is made clear that there were no proxy interviews. It is not possible properly to assess the strengths and weaknesses of this study.

F18. Wang T-J [45]

This case-control study of nonsmoking women aged 35-69 in Shenyang, China involved 135 lung cancer newly diagnosed cases identified in 18 hospitals in 1992-94

and an equal number of controls, matched for age (±5 years), and randomly selected from the general population of the city. Data were collected on ETS exposure at home, at work and in childhood, and on a range of potential confounding variables. One weakness of the study was that there was no insistence on histological confirmation, 43% being diagnosed by signs and symptoms, X-rays and CT films. Also, while controls were, presumably, interviewed at home, cases were interviewed in hospital.

F19. Schwartz [46]

In 1984-87, 5953 Detroit area residents aged 40-84 were identified as having cancer of one of various defined sites. At the same time 3372 population controls aged 40-84 were identified. The data actually collected at the original stage were not stated in ref 46, but clearly included some smoking data as the authors were able to identify 401 lung cancer cases among non-cigarette smokers and 398 nonsmoking controls, frequency matched to the cases by age, sex, race and country of residence. Subsequently an attempt was made to collect further data by telephone interview with identified subjects or their proxies on health history, smoking history, ETS exposure and occupation. After excluding those who proved to have smoked cigarettes, pipes or cigars, who refused to participate, or for whom the subject or a proxy respondent could not be identified, 257 nonsmoking lung cancer cases and 277 nonsmoking population controls were studied. The main interest of ref 46 was family history of lung cancer, data being collected also from over 4000 relatives of the subjects. However, limited results, for sexes combined, on the association between lung cancer and ETS exposure at home and at work were reported. One major limitation of the study is that the frequency of proxy response varied markedly between cases, 83%, and controls, 22%. Another problem was that, though the family history relative risks were adjusted for quite a wide range of potential confounding variables, the ETS results were only adjusted for age, sex and race.

APPENDIX G

Estimating the significance of dose-related trends with and without the unexposed group

Tables 5, 6 and 7 present available data on relative risks of lung cancer among lifelong nonsmoking women in relation to, respectively, number of cigarettes per day smoked by the husband, years of exposure to smoking from the husband, and pack-years of exposure from the husband. These data are adjusted for covariates, if adjusted data are given.

Although some authors present the results of trend tests including the unexposed group, some authors do not. Furthermore results are not generally presented of trend tests excluding the unexposed group, which some have suggested [76] may be more appropriate. We therefore calculated the significance of trend tests including and excluding the unexposed group in a consistent way, and marked those that were significant (two-tailed $p<0.05$) in Tables 5, 6 and 7.

The calculation of the trends is as described by Breslow and Day [76]. Given data on numbers of cases and controls by level of exposure as follows:

	Exposure level		
	1	2 . . . . . k	Totals
Cases	a_1	a_2 . . . . . a_k	n_1
Controls	c_1	c_2 . . . . . c_k	n_0
Totals	m_1	m_2 . . . . . m_k	N

and defining e_i as the expected number of cases at level i (i=1...k) assuming no treatment relationship, x_i as the "dose" at level i, and Z as the trend statistic, we have:

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Install Equation Editor and double-click here to view equation. (2)

Install Equation Editor and double-click here to view equation. (3)

so that the chisquared for trend is

Install Equation Editor and double-click here to view equation. (4)

This formula, without continuity correction, was used with "doses", x_i, set equal to i. It was applied using all the groups or deleting the unexposed group.

Table G1 shows the data used in the dose-response analysis. As can be seen in that table, some of the studies provide data in the required format of numbers of cases and controls at each of the exposure levels. Other studies do not provide the data in this format and it was necessary to estimate the data table and hence the trend and its significance.

Especially where relative risks are adjusted for covariates, the authors (e.g. Garfinkel 1) often present their data in the form of numbers of cases and relative risks at each level, coupled with the total number of controls. Here effective numbers of controls by level could be estimated using the formulae $\Sigma c = n_0$ and $r_i = a_i c_1 / a_1 c_i$ (where r_i is the relative risk for level i).

In still other studies (e.g. Wu) the only data given were the total numbers of cases and controls and the relative risks. Here the data required were estimated assuming the numbers of controls were equal at each level. In some studies (e.g. Stockwell) one had information on relative risks and on total numbers of unexposed and exposed cases and controls but not on numbers of exposed cases and controls by level. Here it usually proved impossible to produce numbers by level satisfying all the restrictions. Here we first estimated the control data, assuming numbers of exposed controls at each level were equal, and then used the relative risks to construct the case data (ignoring the known number of unexposed cases). In one or two other studies, still further procedures were used. For the Sun study, estimation of the trend proved impossible, but it seemed apparent it was not significant.

The general aim of the procedure was to derive a 2xk table of numbers of cases and controls with precisely the cited relative risks and the total numbers of cases and controls correct. It was believed this would allow estimation of the trend statistics reasonably accurately. Precise estimation of the trend statistics would require, for the adjusted data, more detailed data than are normally presented in the source papers.

Table G2 shows the estimated values of the trend chisquared statistics, values above 3.84 being taken as statistically significant. Detailed output from the program written to complete the data arrays and calculate the trends is available on request.

From these tables the following conclusions can be reached:

Cigarettes per day

Using the trend including the unexposed group, significant ($p<0.05$) positive trends are seen in six out of the 19 studies. In one study (Inoue) the trend was reported by the authors as significant but our calculations give $0.05<p<0.1$. For four of the six significant studies (Trichopoulos, Hirayama, Lam T, Geng) excluding the unexposed group made the trend non-significant. The Lam T study in particular shows a marked increase in risk in women married to a smoker, but no evidence at all that risk increased with amount smoked by the husband. In only two of these six studies (Garfinkel 2, Liu Q) did the trend remain significant after excluding the unexposed group. In both of these, the significance resulted from the high risk in the highest exposure group, with no evidence of an increase at lower exposures. There were two studies (Pershagen, Du) where the trend was only significant if the unexposed group was excluded. In both these studies, an elevated risk was only seen in the highest exposure group.

Years of exposure

Including the unexposed group, significant positive trends were seen in two of the 15 studies where estimation was possible. When the unexposed group was excluded the trend became non-significant in both these studies (Gao, Geng) and in fact was not significant in any study. In the study by Stockwell, the authors reported the trend as significant, but again our calculations give $0.05<p<0.1$.

Pack-years of exposure

Of the five studies, significant trends including the unexposed group were seen in two (Correa, Fontham) and significant trends excluding the unexposed group in one (Brownson 2). In the Brownson 2 study, the significance arose because relative risks were elevated in the highest exposure group but decreased in the other two exposed groups.

Although the overall data indicate a tendency for risk to be highest in those with highest exposure, it is notable that there are no studies where the relative risks increase in a strictly monotonic fashion across all the groups and the trend excluding the unexposed group is significant. It should be noted, however, that the power to detect significant trends will be substantially lower when the unexposed group is excluded.

TABLE G1

Data for dose-response analysis

Study		Unadjusted data					Covariate adjusted data				
Ref	Author/ exposure	By level				Total	By level				Total
1	Garfinkel 1	65	39	49			65	39	49		
	C	1.00	1.27	1.10		176739	1.00	1.37	1.04		176739
3	Correa	8	5	9							
	P	72	38	23							
4	Trichopoulos	24	15	24	14						
	C	109	35	56	25						
5	Buffler	8	10	23							
	Y	32	65	99							
6	Hirayama	37	99	64			37	99	64		
	C	21895	44184	25461			1.00	1.43	1.74		91540
8	Garfinkel 2	43	11	32	30						
	C	148	45	102	52						
10	Wu	*	*	*		29					
	Y	1.0	1.2	2.0		62					
11	Akiba	21	29	22	12		21	29	22	12	
	C	82	90	54	23		1.0	1.3	1.5	2.1	249
11	Akiba	21	20	29	22		21	20	29	22	
	Y	82	30	81	59		1.0	2.1	1.5	1.3	252
14	Gao	57	63	78	48		57	63	78	48	
	Y	99	93	107	76		1.0	1.1	1.3	1.7	375
15	Humble						5	*	*		15
	C						71	1.8	1.2		91
15	Humble						5	*	*		15
	Y						71	1.6	2.1		91
16	Koo	32	17	25	12		32	17	25	12	
	C	67	15	35	19		1.00	2.33	1.74	1.19	136
16	Koo	22	20	24	22		22	20	24	22	
	Y	40	28	39	30		1.00	1.95	1.36	2.26	137
17	Lam T	84	22	56	20						
	C	183	22	66	21						
18	Pershagen						34	26	7		
	C						1.0	1.0	3.2		294
20	Geng	20	*	*	*	34					
	C	52	1.40	1.97	2.76	41					
20	Geng	20	*	*	*	34					
	Y	52	1.49	2.23	3.32	41					
21	Inoue	4	3	15			4	3	15		
	C	17	11	19			1.00	1.58	3.09		47
23	Choi	26	6	31	12						
	Y	76	12	61	15						
24	Hole						1	2	3		

G6

C		1.00	0.78	1.78	1784

TABLE G1 (continued)

Data for dose-response analysis

Study		Unadjusted data					Covariate adjusted data					
Ref	Author/ exposure	By level				Total	By level					Total
26	Janerich						68	*	*			76
	Y						58	0.63	0.79			86
26	Janerich						68	*	*	*		76
	P						58	0.54	0.90	0.82		86
27	Kalandidi	26	34	22	8							
	C	46	39	22	9							
27	Kalandidi	26	15	15	17	17						
	Y	46	21	20	15	16						
32	Brownson 2	213	32	54	110		213	32	54	110		
	P	568	128	200	216		1.0	0.7	0.7	1.3		1112
33	Stockwell						18	*	*	*		44
	Y						36	1.6	1.4	2.4		55
34	Liu Q	13	6	19			13	6	19			
	C	32	21	16			1.0	0.7	2.9			69
35	Du	28	13	30								
	C	100	69	72								
35	Du	28	14	29								
	Y	100	37	96								
36	Fontham	153	184	143	173		153	184	143	173		
	Y	321	393	244	295		1.00	1.10	1.33	1.23		1253
36	Fontham	267	146	92	80	24	267	146	92	80	24	
	P	562	300	190	126	27	1.00	1.08	1.04	1.36	1.79	1205
37	Cardenas	51	8	15	2		51	8	15	2		
	C	521062	61820	126087	45836		1.0	1.4	1.4	0.6		754805
37	Cardenas	30	13	14	17		30	13	14	17		
	Y	334946	107681	112761	114002		1.0	1.5	1.3	1.2		669390
37	Cardenas	30	10	16	18		30	10	16	18		
	P	334946	112318	113119	109006		1.0	1.1	1.3	1.5		669389
38	Layard	24	5	8	0		24	5	8	0		
	C	969	336	405	111		1.00	0.54	0.76	0.00		1821
40	Kabat 2	26	17	12			26	17	12			
	C	71	50	28			1.00	0.82	1.06			149
43	Sun						*	*	*			230
	Y						1.00	?	0.86			230
45	Wang T-J	43	4	45	43							
	C	49	13	38	35							
45	Wang T-J	65	21	32	17							
	Y	70	16	32	17							

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references.

Exposures are C = cigarettes per day, Y = years, P = pack-years; see Tables 5 to 7 for the actual groupings used.

For each study, the top line of data concerns numbers of lung cancer cases, while the second concerns numbers of controls (or at risk for prospective studies) or relative risks (if given as decimal numbers). Asterisks indicate data not available.

TABLE G2

Estimated trend chisquared values and their significance

Study		Unexposed group included		Unexposed group excluded	
Ref	Author	Trend Chisquared	Significance	Trend Chisquared	Significance
Cigarettes per day smoked by husband					
1	Garfinkel 1	0.100		(1.658)	
4	Trichopoulos	6.687	+	0.314	
6	Hirayama	7.210	+	1.497	
8	Garfinkel 2	4.166	+	5.412	+
11	Akiba	3.148		1.218	
15	Humble	0.159		(0.456)	
16	Koo	1.009		(1.787)	
17	Lam T	10.145	+	(0.016)	
18	Pershagen	1.854		5.092	+
20	Geng	5.653	+	1.348	
21	Inoue	3.304		0.792	
24	Hole	0.497		0.860	
27	Kalandidi	1.936		0.033	
34	Liu Q	4.925	+	6.384	+
35	Du	1.560		4.641	+
37	Cardenas	0.266		(0.805)	
38	Layard	(2.681)		(0.289)	
40	Kabat 2	(0.000)		0.335	
45	Wang T-J	2.059		3.000	
Years of exposure to smoking from the husband					
5	Buffler	0.035		1.009	
10	Wu	1.639		0.892	
11	Akiba	0.350		(1.575)	
14	Gao	4.552	+	2.834	
15	Humble	1.709		0.220	
16	Koo	3.047		0.126	
20	Geng	7.943	+	1.909	
23	Choi	3.632		0.753	
26	Janerich	(0.959)		0.503	
27	Kalandidi	3.377		1.080	
33	Stockwell	3.465		0.777	
35	Du	0.064		(0.353)	
36	Fontham	3.361		0.785	
37	Cardenas	0.491		(0.357)	
43	Sun		Not estimable		
45	Wang T-J	0.074		(0.335)	
Pack-years of exposure from the husband					
3	Correa	5.127	+	3.245	
26	Janerich	(0.279)		0.972	
32	Brownson 2	0.940		10.744	+
36	Fontham	5.151	+	3.411	
37	Cardenas	2.047		0.633	

Footnotes

G9

The study author is the name of the first author in the publication from which the data were extracted; see references.
The trend chisquared values are estimated using the data in Table G1; chisquared values relating to negative trends are shown in brackets.
Significant ($p<0.05$) positive trends are indicated by +; no significant negative trends were seen.

APPENDIX H

Relative risks of lung cancer for other indices of exposure

Introduction

Some studies provide results for more than one index of exposure to smoking by the husband. Where there is a choice, the data presented in Table 2 relate to the index nearest to "husband ever smoked" as this is the index most commonly used in the studies. Table H1 presents results for the additional indices not used in Table 2. It also shows, in brackets, some limited data relating to additional indices of exposure to smoking by the wife.

Some studies have provided data relating to more than one index of exposure to ETS exposure in childhood. Where there is a choice, the data presented in Table 18 are based on any household exposure if available or smoking by the mother if not. Table H2 presents results for the additional indices not used in Table 18. It also shows, in brackets, the result for the index actually used in Table 18.

TABLE H1

Relative risk of lung cancer among lifelong nonsmoking women in relation to other aspects of smoking by the husband

Study Ref	Author	Location	Aspect/ Grouping		Relative risk by grouping	Significance (trend)
8	Garfinkel 2	USA	Husband at home cigs/day			
			None <10 10-19 20+		1.00 1.15 1.08 2.11	+
12	Lee	UK	Husband smoked man cigs in last 12 months			
			No Yes		1.00 0.76 (0.96)	
			Husband smoked man cigs in whole of marriage			
			No Yes		1.00 0.55 (2.47)	
19	Butler	USA	Current smoking of husband			
			Never Past Current		1.00 1.69 3.37	
32	Brownson 2	USA	Pack-Years x hrs/day			
			0 1-50 51-175 176+		1.0 0.7 0.8 1.3	
			Exposure to passive smoking			
			0 Light Moderate Heavy		1.0 ? ? 1.8	
36	Fontham	USA	Type of tobacco smoked by husband			
			Cigarettes Cigars Pipes		1.18 1.25 1.19	
37	Cardenas	USA	Husband smokes;			
			Current any:	No Yes	1.0 1.3 (1.0)	
			Former any:	No Yes	1.0 1.1 (1.1)	
			Ever cigarettes:	No Yes	1.0 1.1 (1.0)	
			Current cigarettes:	No Yes	1.0 1.3 (1.0)	
			Former cigarettes:	No Yes	1.0 1.2 (1.1)	
			Ever cigars/pipes:	No Yes	1.0 1.1	
			Current cigars/pipes:	No Yes	1.0 1.5	
			Former cigars/pipes:	No Yes	1.0 1.3	
			Amount formerly smoked by husband			
			0 1-19 20-39 40+		1.0 0.8 0.8 1.5 (1.0 0.6 1.0 1.2)	
40	Kabat 2	USA	Spouse smokes in bedroom			
			No Yes		1.00 1.09 (5.02)	
			No/nonsmoker Yes		1.00 1.07 (2.67)	

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
In study 32 results only given for heavy exposure to passive smoke.
In studies 12, 37 and 40 data given in brackets relate to smoking by the wife.
Relative risks presented are adjusted for covariates if adjusted data are available.
See Appendix B for details of how the data were extracted from the source publication.
See Appendix C for the covariates considered in the adjusted analyses.
Significant ($p < 0.05$) positive relative risks are indicated by +.

TABLE H2

Relative risk of lung cancer among lifelong nonsmoking women in relation to other indices of ETS exposure in childhood

Study					
Ref	Author	Location	Index of exposure	Relative risk (95% CI)	Significance
25	Svensson	Sweden	(Mother)	3.30(0.50-18.8)	
			Father	0.90 (0.40-2.30)	
28	Sobue	Japan	(Mother)	1.28(0.71-2.31)	
			Father	0.79 (0.52-1.21)	
			Other household members	1.18(0.76-1.84)	
32	Brownson 2	USA	(Any household member)	0.80(0.60-1.10)	
			Parents	0.70 (0.50-0.90)	–
36	Fontham	USA	(Any household member)	0.89(0.72-1.10)	
			Father	0.83 (0.67-1.02)	
			Mother	0.86 (0.62-1.18)	
			Other household member	1.03 (0.80-1.32)	
43	Sun	China	(Childhood)	2.29(1.56-3.37)	+
			In adolescence	2.60(1.77-3.83)	+
			Mother	2.05(1.29-3.27)	+
			Father	2.35(1.56-3.54)	+

Footnotes
The study author is the name of the first author in the publication from which the data were extracted; see references.
Where the index of exposure is in brackets the data presented are those given in Table 18.
Relative risks presented are adjusted for covariates if adjusted data are available.
See Appendix B for details of how the data were extracted from the source publication.
See Appendix C for the covariates considered in the adjusted analyses.
Significant ($p < 0.05$) positive relative risks are indicated by + and significant ($p < 0.05$) negative are indicated by – .

H4

APPENDIX I

Trying to explain between-study variation in relative risk estimates in relation to marriage to a smoking husband

Table 2 of the main body of this report gives relative risks and 95% confidence limits for 44 studies of lung cancer in nonsmoking women in relation to smoking by the husband. Although the combined relative risk, using fixed effects meta-analysis, and covariate-adjusted data where available, is statistically significant (1.16, 95% CI 1.09-1.25), the 44 estimates are statistically heterogeneous ($p<0.001$). What is the reason for this heterogeneity? The report discusses a range of possible sources of heterogeneity and shows that, for a number of them, there is significant variation between the relative risk estimates. However, many of these sources are correlated, and it is of interest to carry out a multiple regression analysis to determine the major sources.

The program GLIM (general linear interactive modelling) was used to carry out a weighted multiple regression. Taking R, RU and RL as, respectively, the relative risk and the upper and lower 95% confidence limits, the regression was on log R, with weights equal to the inverse of the variance of log R, the standard error of log R being estimated by (log RU - log RL) / 3.92.

Ten factors were used to predict log R:

YRG	Grouped year of publication	1 = 1981-86	(12 studies)
		2 = 1987-89	(13)
		3 = 1990-92	(8)
		4 = 1993-96	(11)
LOC	Location	1 = Western Europe	(5)
		2 = USA	(17)
		3 = Japan	(5)
		4 = China/Korea	(10)
		5 = Hong Kong	(4)
		6 = Greece and Russia	(3)
TYP	Study type	1 = Prospective	(5)
		2 = Case/healthy control	(16)
		3 = Case/diseased control	(20)
		4 = Other case-control	(3)

NLG	Number of lung cancer cases grouped	1 = <50	(14)
		2 = 50-100	(15)
		3 = 101+	(15)
HIS	100% histological confirmation	1 = No	(25)
		2 = Yes	(19)
QUA	Study quality	1 = "Inferior"	(21)
		2 = "Superior"	(23)
CON	Adjustment for confounders	1 = Yes	(28)
		2 = No	(16)
DOS	Dose-response analysis conducted	1 = Yes	(28)
		2 = No	(16)
SPO	Index of exposure	1 = Spousal smoking	(36)
		2 = Other index	(8)
AGE	Age adjustment/matching	1 = No	(12)
		2 = Yes	(32)

Table I1 summarizes the results of some of a large number of regression analyses carried out. The deviance (chisquared) with no factors included at all was 77.75 on 43 d.f. ($p<0.001$), and the first column of results shows the effect of introducing each factor in turn, corresponding to the meta-analysis for the various factors shown in Table 3 of the main body of the report. Thus, introducing YRG into the model reduced the deviance by 24.13 on 3 d.f., $p<0.001$, with relative risks for the four levels estimated as exp (0.2560) = 1.29, exp (0.2560 + 0.1205) = 1.46, exp (0.2560 - 0.3442) = 0.92 and exp (0.2560 - 0.0491) = 1.23. (The estimate presented under the first level is the mean for the factor-specific analysis, to which the other estimates should be added for studies in levels 2, 3 and 4.) It can be seen that, ignoring the other factors, three of the factors (YRG, CON and AGE) were highly significant ($p<0.001$), two (LOC and DOS) were quite highly significant ($p<0.01$) and three (TYP, NLG and HIS) were also significant (at $p<0.05$).

Based on selecting the factors which reduced the mean deviance most, one could select best models as follows:

	Deviance	D.F.	Mean deviance

No factor included		77.75	43	1.808
One factors included	- YRG	53.62	40	1.340
Two factors included	- YRG, LOC	39.60	35	1.131
Three factors included	- YRG, LOC, QUA	35.03	34	1.030
Four factors included	- YRG, LOC, QUA, AGE	31.30	33	0.948

Results for the four factor model are also shown in Table I1, the chisquared being estimated from the difference between the four factor model above, and that excluding the model in question. It can be seen that in the four factor model, YRG and LOC were reduced in significance but remained significant at $p<0.01$ and $p<0.05$ respectively. AGE was also reduced in significance compared to the one factor model, and was now not quite significant ($0.05<p<0.1$). QUA remained not quite significant ($0.05<p<0.1$).

It can be seen that the best two factor model was a considerable improvement over the null model, reducing the deviance by 38.15 on 8 d.f. ($p<0.001$), but that the further introduction of QUA and AGE was more marginal. In fact there was no longer real heterogeneity once YRG and LOC were introduced, though the effect of introducing QUA and AGE was significant (with the deviance reducing by 8.30 on 2 d.f. ($p<0.05$).

Further introduction of factors did not reduce the deviance much, and the adequacy of the four factor model (in a statistical sense) was emphasized by consideration of the residuals, the largest seen being

Layard	- 2.324	S.E.
Chan	- 1.881	S.E.
Wang S	+1.868	S.E.

values which did not suggest the existence of outliers.

If one included all the factors in the model, the deviance reduced to 23.53 on 24 d.f. Results for this full model are also shown in Table I1. It is interesting to note that when the significance of each of the factors in the full model was assessed (by comparing the deviance for

the full model with the deviance for the model including all the factors but the one in question) only one factor, QUA, remained significant at $p<0.05$, though a number of factors (LOC, NLG, HIS and AGE) were almost significant ($0.05<p<0.1$). It was particularly interesting to note that two factors which were highly significant in the one factor models (YRG and CON) were not at all significant in the full model, implying that the simple associations could be explained by other correlated factors.

Because YRG was not significant in the full model, and because, by its nature, it seemed more likely to be a correlate rather than a true cause of variation in relative risk, additional analyses were carried out excluding YRG as a factor. Here the successive models chosen were:

		Deviance	D.F.	Mean deviance
No factor included		77.75	43	1.808
One factors included	- LOC	57.56	38	1.515
Two factors included	- LOC, AGE	45.03	37	1.217
Three factors included	- LOC, AGE, DOS	40.74	36	1.132
Four factors included	- LOC, AGE, DOS, HIS	35.28	35	1.008

Again, introducing further factors did not materially reduce the deviance.

The results of these analyses do not clearly show which factors cause the heterogeneity. Clearly all the significant associations seen in the one factor at a time analyses do not represent independent relationships but equally clearly there appear to be a number of independent relationships. Whatever the reason for the heterogeneity, it is apparent that it is large compared to the overall relative risk associated with marriage to a smoker. In the four factor model shown in Table I1, the estimated ratios of relative risk between the highest and lowest levels of the factors are, respectively:

YRG - 1987-89 vs 1990-92	1.41
LOC - Greece/Russia vs China/Korea	1.69
QUA - Inferior vs Superior	1.18
AGE - No adjustment vs Adjustment	1.30

This compares with an overall relative risk estimate of only 1.16 for marriage to a smoker.

TABLE I1

Multiple regression analyses of factors associated with the relative risk of lung cancer relating to smoking by the husband

	One factor model		Four factor model		Full model	
	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Mean*			0.5602	0.2590	1.2220	0.4850
YRG (1)	0.2560	0.0879	-	-	-	-
(2)	0.1205	0.1339	0.1046	0.1314	0.0183	0.1607
(3)	-0.3442	0.1136	-0.2389	0.1150	-0.1275	0.1570
(4)	-0.0491	0.1143	-0.0269	0.1139	0.0306	0.1368
χ^2_3, p	24.13, p<0.001		11.43, p<0.01		1.70, N.S.	
LOC (1)	0.2565	0.2385	-	-	-	-
(2)	-0.1449	0.2468	-0.0815	0.2173	-0.2846	0.2769
(3)	0.0047	0.2725	0.1788	0.2247	0.0634	0.2809
(4)	-0.2596	0.2528	-0.1637	0.2190	-0.1979	0.2441
(5)	0.1184	0.2844	-0.1556	0.2460	-0.2636	0.2848
(6)	0.3580	0.2992	0.3627	0.2593	0.2770	0.3073
χ^2_5, p	20.19, p<0.01		14.92, p<0.005		10.13, p<0.1	
TYP (1)	0.2110	0.1202			-	-
(2)	-0.1523	0.1348			-0.3510	0.1927
(3)	0.0836	0.1490			-0.4796	0.2207
(4)	0.1235	0.3207			-0.4525	0.3415
χ^2_3, p	9.50, p<0.05				4.72, N.S.	
NLG (1)	0.2167	0.1743			-	-
(2)	0.1417	0.2023			0.0865	0.1798
(3)	-0.1262	0.1821			-0.1522	0.1879
χ^2_2, p	9.25, p<0.05				3.11, p<0.1	
HIS (1)	0.0861	0.0597			-	-
(2)	0.1614	0.0940			0.1906	0.1132
χ^2_1, p	5.11, p<0.05				2.78, p<0.1	
QUA (1)	0.2180	0.0688	-	-	-	-
(2)	-0.1239	0.0938	-0.1613	0.0872	-0.2723	0.1231
χ^2_1, p	3.11, p<0.1		3.25, p<0.1		4.80, p<0.05	
CON (1)	0.0799	0.0497			-	-
	0.3021	0.1022			-0.0816	0.1897
χ^2_1	13.39, p<0.001				0.18, N.S.	
DOS (1)	0.2147	0.0555			-	-
(2)	-0.1953	0.0973			-0.0128	0.1504
χ^2_1, p	6.81, p<0.01				0.01, N.S.	
SPO (1)	0.1549	0.0495			-	-
(2)	-0.0498	0.1822			-0.1646	0.1896

χ_1^2, p		0.14, N.S.				0.74, N.S.	
AGE	(1)	0.4276	0.1049	-	-	-	-
	(2)	-0.3339	0.1153	-0.2639	0.1330	-0.3912	0.2085
χ_1^2, p		12.94, p<0.001		3.73, p<0.1		3.45, p<0.1	

*By “mean” is meant the estimate corresponding to a study with factors all at level 1.

APPENDIX J

Potential for bias due to failure to age adjust in studies where some age matching has occurred

In a number of ETS/lung cancer case-control studies, no explicit age-adjustment has been carried out, reliance being placed on age-matching despite the fact that the age-matching is of all cases and controls (regardless of smoking) and the ETS analyses are typically based on never smoking cases and controls.

Let us consider a scenario in which there are two birth cohorts, in one of which smoking by men is common (80%) and by women is relatively uncommon (20%), and in the other of which smoking by men and women are similarly common (at 50%). Assuming similar concordance ratios of husband/wife smoking habits in each cohort, one might have joint distributions of smoking habits in the two populations of:

			Male		
			No	Yes	
Cohort 1	Female	No	18	62	80
		Yes	2	18	20
			20	80	

Concordance = 2.61

			Male		
			No	Yes	
Cohort 2	Female	No	31	19	50
		Yes	19	31	50
			50	50	

Concordance = 2.66

Suppose we have a study in which we select 1000 lung cancer cases from each cohort and age-match by selecting 1000 controls from the corresponding controls. We would now expect to see the following distribution of the control females:

Smoking group	Cohort 1	Cohort 2	Total
Non-smoker - married to non-smoker	180	310	490
- married to smoker	620	190	810
- total	800	500	1300
Smoker	200	500	700

Let us now assume that (i) the true smoker/non-smoker relative risk is 8.0 and (ii) the true relative risk for marriage to a smoker is 1.0. It is then easy to compute the expected distribution of the case females:

Smoking group	Cohort 1	Cohort 2	Total
Non-smoker - married to non-smoker	75.00	68.89	143.89
- married to smoker	258.33	42.22	300.56
- total	333.33	111.11	444.44
Smoker	666.67	888.89	1555.56

From these tables one can calculate the following relative risks within cohorts.

Cohort 1

Smoker/non-smoker $\frac{666.67 \times 800}{333.33 \times 200} = 8.00$

Marriage to smoker $\frac{258.33 \times 180}{75.00 \times 620} = 1.00$

Cohort 2

Smoker/non-smoker $\frac{888.88 \times 500}{111.11 \times 500} = 8.00$

Marriage to smoker $\frac{42.22 \times 310}{} = 1.00$

68.89 x 190

These are all equal to the true values, being calculated within the cohort (i.e. age-adjusted).

However, if one ignores cohort and computes the relative risks based on the totals one gets:

Smoker/non-smoker $\frac{1555.56 \times 1300}{444.44 \times 700} = 6.50$

Marriage to smoker $\frac{300.56 \times 490}{143.89 \times 810} = 1.26$

Here one underestimates the smoker/non-smoker relative risk and obtains a spurious positive relative risk associated with marriage to a smoker.

The bias in the estimate of the smoker/non-smoker relative risk arises despite the fact that the controls have been selected to have the same cohort distribution as the cases. Breslow and Day [76] note (on p 103) that "variables which have been used for matching in the design should be incorporated in the analysis as confounding variables."

The bias in the estimate of the relative risk associated with marriage to a smoker arises without making any assumptions about lung cancer risk varying by age (cohort). It has arisen because the distribution of smoking habits and exposure to ETS was assumed to vary by age.

If, in fact, there was no initial matching at all, the bias could be greater. Suppose, for example, that the two cohorts occurred equally in the living population, but that, among cohort 1 (earlier and older) overall lung cancer incidence was five times higher than among cohort 2. Suppose, as before, we sampled 1000 controls from each cohort, but that we now had 5000 cases from cohort 1 and 1000 from cohort 2. The expected distribution of the cases would now be:

Smoking group	Cohort 1	Cohort 2	Total
Non-smoker - married to non-smoker	375.00	68.89	443.89
- married to smoker	1291.67	42.22	1333.89
- total	1666.67	111.11	1777.78
Smoker	3333.33	888.89	4222.22

Here, computing unadjusted relative risks based on the totals, one gets:

Smoker/non-smoker $\frac{4222.22 \times 1300}{1777.78 \times 700} = 4.41$

Marriage to smoker $\frac{1333.89 \times 490}{443.89 \times 810} = 1.82$

Here the biases are increased. The relative risk for smoking is underestimated because smokers are assumed to form a larger proportion of the younger than the older cohort, and because risk of lung cancer is assumed to be lower in the younger cohort. The relative risk for marriage to a smoker is overestimated because marriage to a smoker is commoner in the older cohort where lung cancer risks are higher.

In practice the magnitude and direction of the bias would depend on the extent to which smoking, marriage to a smoker, and lung cancer risk varied with age and on the exact way cases and controls were selected. There is clearly, however, a considerable potential for bias when age adjustment is not carried out.